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EXPERIMENTAL AND PATHOLOGICO-ANATOMICAL RESEARCHES ON THE CORPUS CALLOSUM.[1]

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INTRODUCTION.

ON separating the two fore-brain hemispheres of any mammal, the corpus callosum becomes visible; its position between the two halves of the brain at once suggests that it serves as a connecting link between the hemispheres.

There is no doubt that certain bundles exist in this mass of fibres, the origin and termination of which lie on the same side of the middle line. These are the fibres which belong, in the wide sense of the term, to the olfactory system, i.e., the fornix longus, tænia tecta, and the nervi Lancisii. These fall outside the province of this research, which is confined to what is commonly understood as the corpus callosum, that is to say, the chief interhemispherical commissure of the neopallia.

The term commissure may either be understood to mean a connexion of corresponding regions of the opposite hemispheres; or, taking it in a broader sense, a connexion in general of the one half of the brain with the other, through which both homotopical and heterotopical cortical regions are associated with each other. To give the word its full meaning it connotes an interhemispherical association system.

Both interpretations are found in the literature, though it is not possible to state that they always rest upon conclusive anatomical or pathological evidence. The more modern writers embrace the latter opinion on the whole, chiefly on the strength of Cajal's histological investigations; in small mammals, as the mouse, with the aid

[1] Dedicated to Professor von Monakow.

of his silver methods, Cajal found that from cortical cells axones arise, which either directly or as collaterals of projection and longer association neurons, pass to homo- and heterotopical points of the opposite hemisphere through the corpus callosum [4].

I believe that this conclusion concerning the ending of the callosal fibres cannot be positively proved from normal silver preparations. Moreover, were normal histological investigations sufficient to place Cajal's theory beyond all question, they afford very little evidence of the "associative" nature of the commissure. Cajal believes that the callosal fibres give off collaterals before ending, but these can be followed with certainty over very insignificant distances only in one section. Though strictly speaking the term association may be applicable to such a connexion, it approaches more nearly to what one may consider as a commissure. In any case it is evident that Cajal's theories, although they may be perfectly correct, by no means justify the frequent assumption that heterotopical cortex regions of both hemispheres stand in connexion by callosal fibres with each other (Ascenzi [2] and others).

In addition to Cajal's and Kölliker's [20] histological results certain morphological investigations support this view. Dejerine cites Schnopfhagen's [44] investigations in proof of heterotopical connexions, but it need hardly be said that the antiquated and highly uncertain "Abfaserung" methods of this writer cannot assist in the solution of the point at issue.

Other methods that have been employed to solve this problem may be briefly considered.

(1) *Teratological cases.*—Agenesis of the corpus callosum has afforded little information on the normal course of the callosal fibres. In the first place there are generally other developmental disturbances in the brain which make it very difficult to arrive at definite conclusions; and when no other disturbances are present, the difficulty remains as to whether the corpus callosum was actually absent, or whether it had not reached the opposite hemisphere. This question is closely connected with the significance of the so-called "Balkenlängsbundel" (Probst [40]). As regards the extensive literature on this subject, I refer for instance to Marchand [29]. The latest contributions to the subject, those of Stöcker [48] and Landsbergen [22], are of no assistance in the solution of our problem.

(2) *Embryology.*—Neither the study of the primary development of the commissural system (His [16], Zuckerkandl [58, 59], Goldstein

[12], Langelaan [23], and others), nor of the myelogenesis of the corpus callosum, have thrown more light on the origin and termination of the commissural fibres.

(3) *Secondary fibre-degeneration.*—The early investigations of Forel [9], v. Gudden [49], and v. Monakow [50] showed that after extensive lesions of one hemisphere, degeneration ensued in the corpus callosum, which could not be followed by v. Gudden's method, nor, as Sherrington [47] and Langley and Grünbaum [24] found, by the method of Marchi, to the cortex of the opposite side. Experimental section of the corpus callosum also threw no light on the course of the fibres. (Muratoff [36], Lo Monaco e Baldi [34], Levy-Valensi [26].) Lo Monaco e Baldi's conclusions chiefly concern the question as to whether the tapetum of the posterior horn in the cat belongs to the corpus callosum. Muratoff concluded that heterotopical connexions are present in the corpus callosum in the dog. Lévy-Valensi agrees with this statement, without, as far as I can see, giving reasonable grounds in support of it.

It is generally accepted that extensive unilateral cortical lesions in the human brain cause atrophy of the corpus callosum, which is practically parallel with the extent of the destruction of the cortex, but Kattwinkel's [18] conclusions are at variance with this. Presumably the cause lies in the final complete disappearance of the degenerated callosal fibres. Exact details concerning the areas of the cortex of the opposite side, which are reached by the degenerated fibres, are, however, rare. It is unnecessary to discuss the views which have been put forward by different authors. According to Anton u. Zingerle [1] a considerable fibre radiation from the frontal lobe of the one hemisphere attains the distal part of the cortex of the opposite side. Probst [41] makes a similar statement. Dejerine's [6] detailed analysis of the callosal fibres and their relation to certain cortical regions is based on cases in which the degeneration of the corpus callosum was probably primary, and is therefore not wholly convincing. On the other hand, one finds of late only one positive assertion that the corpus callosum unites homotopical regions only of both hemispheres (Niessl von Mayendorf [38]), and that is based on the study of degeneration preparations. Similarly, the numerous cases of primary lesions in the corpus callosum have, so far, not contributed to a better knowledge of the manner in which the hemispheres are connected with each other. (Ransom [42], Mingazzini [31], Marie et Guillain [30], Gianelli [11], Ascenzi [2], and others.)

The question as to which cells of the cortex the callosal fibres pass, is briefly considered by Dotto and Pusateri [7]; they place them, from the examination of Marchi preparations, in the third layer, but what these writers mean by the third layer is not certain, and they give no illustration of their preparations.

Lévy-Valensi, after section of the corpus callosum, could trace the degeneration into the layer of the "large pyramids" but not into that of the lesser pyramids. It is not apparent what he desires to convey.

I know of no degeneration investigations on the human brain which have led to any positive result.

(4) *Retrograde cell degeneration* (axonal reaction).—This method has been little employed, either after experimental section of the corpus callosum, or morbid lesions therein, to determine whether cells of any definite region or character show a reaction. Observations on the cortical cells in cases of agenesis of the corpus callosum permit no conclusions. I will discuss later my own findings on the rabbit and cat, and those of de Vries on the mouse.

Thus, our exact knowledge of the interhemispherical callosal fibres is less than one might suppose.

Whether the commissure connects homotopical or heterotopical regions is so far uncertain; from what cells its fibres arise, and about which cells they end is also undetermined. And even the statement that all brain convolutions, except the olfactory region, are connected by the means of the corpus callosum, is open to question. Indeed, in 1891 Beevor [3], in a very careful anatomical study, found that the calcarine cortex of the marmoset monkey is not connected by a commissure with the opposite side. In later publications this theory, if mentioned at all, is considered absurd, but actual proof of its inaccuracy is nowhere to be found.

Equally little of importance is known of the manner in which a possible heterotopical commissure unites the two brain hemispheres. And yet in view of certain clinical and experimental observations of recent years, it is of the highest importance that we should have better information on this matter. I refer here to two groups of clinico-pathological and experimental investigations, namely, Liepmann's [27] study of apraxia callosa, and the effects of section or stimulation of the corpus callosum.

A number of cases have already been published by Hartmann [14], Liepmann u. Maas [28], v. Vleuten [56], Goldstein [13], and others, in which apraxia of the left extremities was probably a result of a lesion

of the connexion of the right hemisphere with the left. The accepted explanation of these motor disturbances was interruption of the connexions between both sensorio-motor zones, in the sense of Heilbronner and Liepmann.

It is remarkable that in not a single case, even when the brain was examined in serial sections, was any light thrown upon the course of this supposed connexion. It need hardly be pointed out that not until we have a better and more accurate knowledge of this connexion shall we be in a position to understand the anatomical basis of apraxia.

Mott's [35] excitation experiments, which seem to indicate that the anterior callosal fibres are in relation to certain parts of the musculature of the body, were put forward by this author as evidence of the existence of a connexion between the motor cortical regions and the giganto-pyramidal cells they contain. Later, neither Korányi [21], Lo Monaco [33], nor Lévy-Valensi could with certainty, even when employing very strong currents, confirm Mott's observations on the dog and monkey. Stimulation in their hands produced no motor effect, and section, as Carville et Duret [5], Muratoff [36], Sherrington [47] and others found, no permanent results.

The explanation of the effect of section of the corpus callosum on the hemianopsia, which occurs for a time in dogs after lesion of the occipital lobe, is equally uncertain. In this respect Korányi's [21] results differ from those of Yoshimura [19].

In each case it seems desirable to control as far as possible the positive or negative results of physiological experiments by recognized anatomical facts. This shall be the aim of my investigation.

Experiments on mice, rabbits, cats, were made in order to trace the origin and the ending of the callosal fibres. Pathological human cases supplied material for the study of the more accurate anatomy of the callosal radiation. The localization of these pathological lesions revealed important details in respect to two regions of the cerebral cortex, the Rolandic zone and the visual sphere. The fact that these two regions are of primary clinical and physiological importance, is ample inducement for the communication of my observations and the reproduction of some preparations.

Experimental Observations.

Different lengths of the corpus callosum were divided sagittally in a number of mice, rabbits and cats, in order to determine from which cell layers of the cerebral cortex callosal fibres arise, and to demonstrate

in which layer of the cortex they end. The result of these investigations has been already published in part [54, 57]. This communication will be referred to for minor details, but the facts obtained by operation on rabbits and cats are here repeated; the changes found in the mouse do not differ essentially from those in the rabbit.

FIG. 1.—Rabbit: normal.

Rabbit.

The section was made either in the median line between the two hemispheres, or close to it. Nissl's and Weigert-Pal's methods were employed in the investigation. For cell changes, that hemisphere in particular was examined which was not injured by the operative lesion.

The corpus callosum was divided either by incising the dorsal surface of the pallium and the white matter, including the corpus callosum beneath it; or a sickle-shaped knife was inserted through the corpus callosum into the lateral ventricle, and then drawn backwards

and forwards through its entire length. This operation causes no other disturbance if the knife is, as far as possible, taken out in exactly the same place as it was inserted. The consequences of such a section is shown in fig. 2. It will be seen that the fibres of the internal capsule and corpus callosum are cut through in the dorso-median part of the right hemisphere.

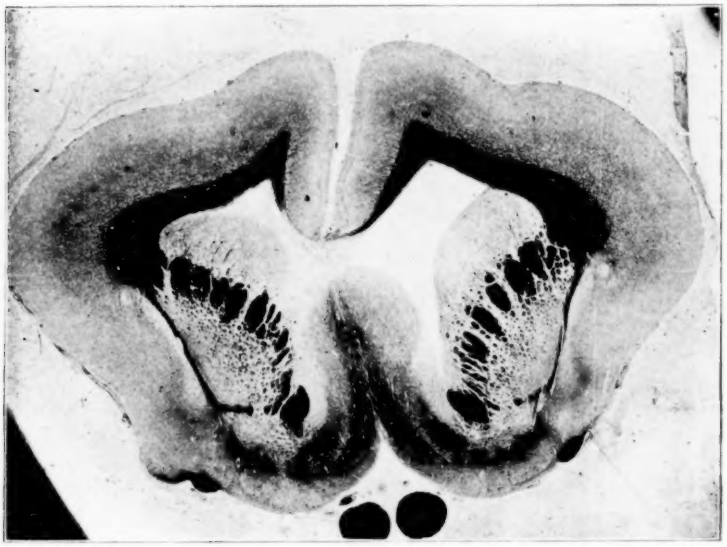

FIG. 2.—Rabbit: section of the corpus callosum in the left hemisphere.

On comparing fig. 2 with a photograph of a normal section at the same level (fig. 1), the smaller bulk of the centrum ovale in the left hemisphere is evident. The part which normally borders the ventricle medio-dorsally and laterally, has disappeared, except a small remnant, which is the fasciculus subcallosus. In the lateral direction the white matter increases rapidly in bulk; this shows that the callosal fibres, shortly after having crossed the median line, pass through the centrum ovale to the cortex. There is no area of degeneration in the central white matter; evidently the normal myelinated fibres come together as the degenerated fibres disappear. I may add that Marchi preparations from other rabbits operated on in the same way, led to the same result as regards the course of the fibres. The degeneration shown up

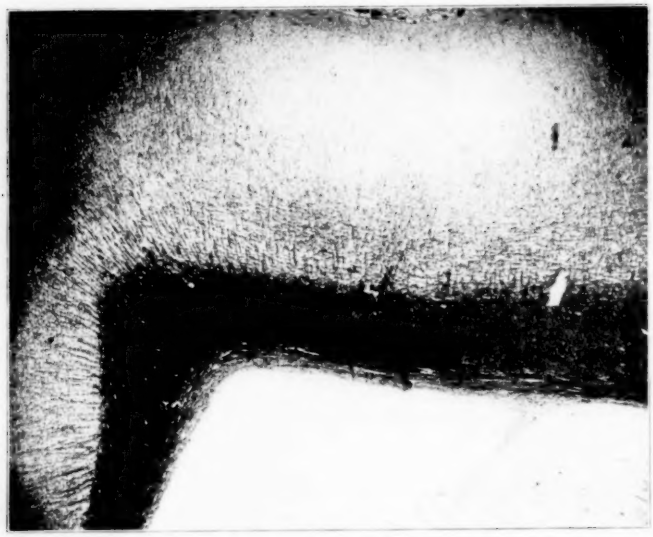

FIG. 3.—Rabbit: division of the corpus callosum in the left hemisphere. Right half of fig. 2; more strongly magnified.

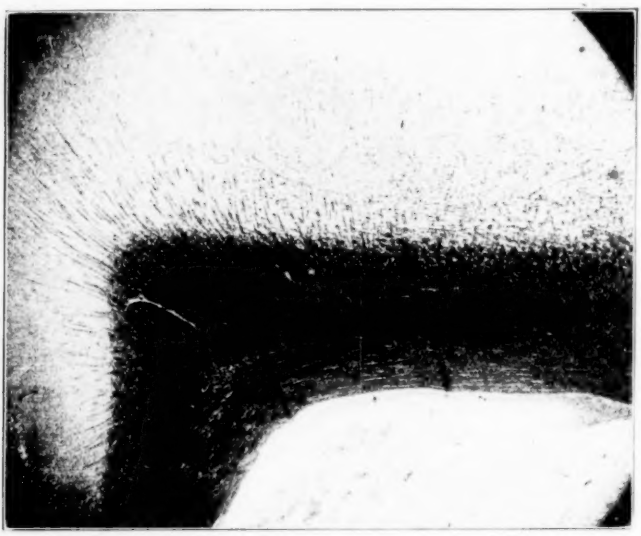

FIG. 4.—Rabbit: normal. Right half of fig. 1.

by this method was, however, unsatisfactory, but it was not in conflict with the observations made on Pal preparations. As the affected callosal fibres must have degenerated to their terminations, one must seek for the evidence of this in the cortex. This is, however, more difficult to find than one would suppose a priori. Indeed, the reader, on comparing the more strongly magnified figs. 3 with 4, without a magnifying glass, will hardly succeed in detecting any difference between the normal cortex and that of the uninjured side in the operated animals. But on closer scrutiny a loss of fibres may be seen in the medio-dorsal cortex in fig. 3. This lies in the regio præcentralis, the area giganto-pyramidalis or field 4 of Brodmann.[1]

The loss affects the radiary fibres in the dorso-median part of the central white matter. There is a diffuse diminution of these fibres, in fact, the somewhat longer ones have entirely disappeared, so that the numerous shorter fibres appear to be unduly separated from each other, but it is not possible to show that these have decreased in number. It is difficult to say to which layer the longer cortical radiations that have disappeared, normally penetrate, because in the area giganto-pyramidalis of the rabbit, the boundaries of the layers are indistinct; the actual "giganto-pyramids" of layer V extend among the pyramidal cells of the more superficial layers, while, as in all animals, the lamina granularis interna is absent. In any case the longest radiating fibres in the normal cortex only penetrate half its depth. These have disappeared in the operated rabbit.

There is also a loss of fibres in the regio post-centralis (field 1 + 3 of Brodmann). In this region, in the normal rabbit, the peculiar comparatively deeply penetrating cortical rays of field 4 do not occur, but short fibres which do not penetrate beyond layer VI, or V, are present in great number; they are moderately thick. Moreover, many fibres coming from the central white matter are cut transversely in frontal sections close to the centrum ovale. Several of these short radiary rays and transverse straight fibres have also disappeared in the uninjured hemisphere. The tangential network of fibres appears to be perfectly intact. The fibre decrease in the cortex of this region is greatest on the dorsal side, and is no longer recognizable on the lateral surface of the hemisphere. The dorso-median part of the normal cortex of this region has no long radiary fibres.

The rest of the dorso-lateral part of the hemisphere is also less

[1] Plate VII from Winkler and Potter: "An Anatomical Guide to Experimental Researches on the Rabbit's Brain," Amsterdam, 1911, may serve for comparison.

rich in coarse fibres than this region in more frontally situated sections. On comparing the uninjured hemisphere of the operated rabbit with the normal, a slight though distinct diminution of these coarse fibres in the inner part of the cortex is apparent.

Further laterally the loss of fibres is of the same character as that described in field 1 + 3.

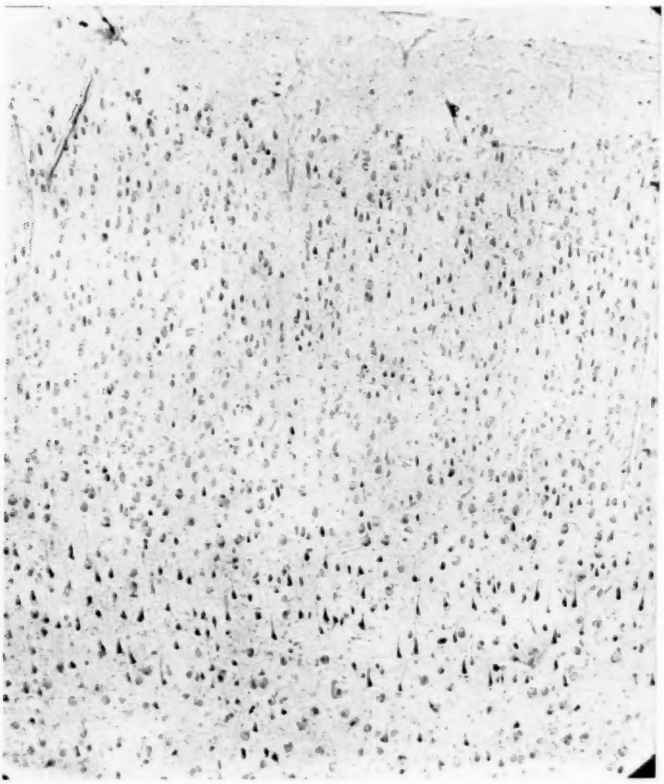

FIG. 5.—Rabbit: normal. Field 1 + 3 (Brodmann). Toluidin blue.

On further comparing preparations from the further occipitalward parts of the cortex of the operated and non-operated animals with each other, the differences are difficult to determine, and it is impossible to show them in a photographic reproduction. Behind the splenium, even microscopic examination cannot detect any perceptible difference.

In order to trace the origin of these fibres, operations were performed in the manner described above and the uninjured hemisphere was examined by Nissl's staining after paraffin imbedding.

It is extremely important to compare the cortex of a rabbit in which cell degeneration is suspected, with a normal series which has been treated in exactly the same way, as the appearance of the

FIG. 6.—Rabbit: divisions of corpus callosum. Field 1 + 3 (Brodmann). Toluidin blue.

cells depends to a great extent upon the manner in which the sections are stained with the toluidin-blue solution. The same cells may appear dark blue and homogeneously coloured in one preparation, and in another pale blue, with only scanty loose protoplasm. It is therefore very easy to mistake degenerations for what is normal. On the other hand, one is very liable, in the cortex of the rabbit, to overlook cell

changes which actually exist; even in regions where fibre preparations show they must exist, often not a trace of them can be found. I have been able to detect them with positive certainty only in Brodmann's fields 4, 1 + 3, 5 + 7. I am unable to illustrate these changes in the area giganto-pyramidalis distinctly in a photograph. De Vries [55] was successful in the mouse, but the alterations in the other fields in this animal were far more distinct.

Fig. 5 shows a transverse section through field 1 + 3 of a normal rabbit, and fig. 6 is from the homologous area of the uninjured hemisphere of a rabbit in which the corpus callosum was cut. There is a distinct pallor in the staining of the large pyramids in layer V (subgranular), and at the same time an apparent decrease of the smaller cells of layer VI, but this is less distinctly visible. The more superficial pyramidal cells (supragranular) are equally developed in both. There is no distinct proliferation of the neuroglia.

These illustrations have been taken from an animal which lived seventy days after the operation; experience teaches that the cell changes show up most clearly about that time. If the animals are allowed to remain alive for one or two years it is extremely difficult to detect any changes; and changes may be visible two or three weeks after the operation. I did not operate on newly born rabbits; according to Nissl [39] callosal lesions, in these animals, produce no appreciable changes, but it seems doubtful if this is correct.

From the experiments upon the rabbit, which are fully confirmed by those on the mouse, the following conclusions may be drawn:—

As far as can be determined the origin of the callosal fibres lies in the subgranular layers of the cortex, and apparently exclusively in that of fields 4, 1 + 3, 5 + 7. In any case there is no reason to suppose any callosal fibres spring from more distant fields. Callosal fibres end in the same regions; the radiation containing callosal fibres in field 4 ascends higher into the cortex than in the remaining fields, in which it does not pass the lamina granularis interna; but it is, of course, possible that they may penetrate higher into the cortex after losing their myeline sheaths.

Whether the callosal connexion is homotopical or heterotopical could not be determined with certainty. Partial cortical lesions of one hemisphere produced, as a rule, only a doubtful cell affection of the cortex on the opposite side, but when a reaction was observed, it was at any rate homotopical. Fig. 7 is from the same cortical area as the former figures (field 1 + 3); the corresponding point of the contra-

lateral hemisphere was extirpated, and it will be observed that there is a moderate decrease of deeply coloured cells in layer V. In the cat a complete sagittal division of the corpus callosum is not possible without considerable injury of the brain. Partial section is, however, possible, and in different experiments all parts of it were cut.

In these investigations the methods of Weigert-Pal with Van Gieson, or of Nissl were employed: the first to trace the secondary degeneration

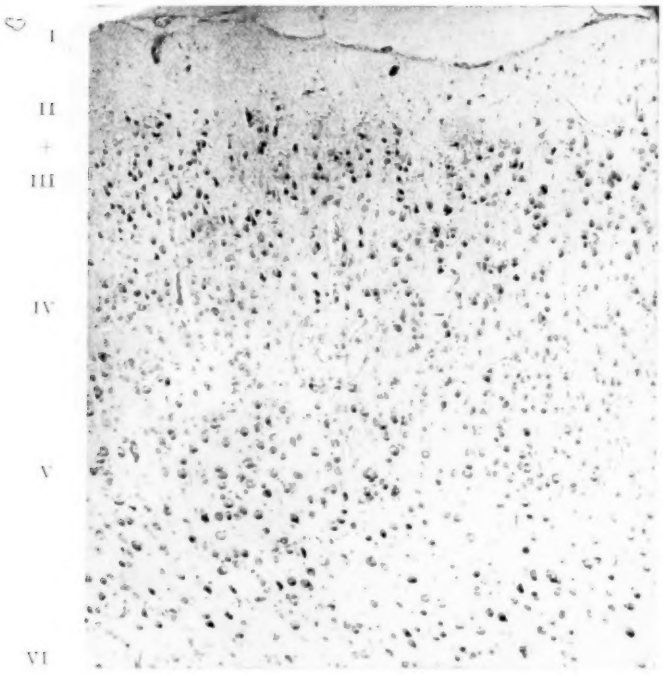

FIG. 7.—Rabbit. Extirpation of field 1 + 3 (Brodmann) in the left hemisphere. Field 1 + 3, right hemisphere. Toluidin blue.

of the fibres, the second in order to demonstrate the reaction in their cells of origin. Marchi's method was of little service; it is certainly inferior to Pal's staining in showing up degenerating or degenerated callosal fibres.

Examination by Marchi's method after section of the frontal part of the corpus callosum gave, as Sherrington has found, more or less

insignificant results. After division of its posterior half, both Pal's and Nissl's methods could be employed with more success.

I will not enter on the much discussed question whether the tapetum ventriculi consists of fibres of the corpus callosum. My results agree on the whole with those of Muratoff and others; the fibre-layer lying immediately above the occipital part of the ventricle consists of thin fibres palely stained by hæmatoxylin (fasciculus subcallosus, Muratoff), which possibly stand in connexion with the nucleus caudatus and the subependymal grey matter. They degenerate partially on the side of the lesion particularly when the nucleus caudatus is injured, and they remain intact on the uninjured side. Close to the median line all the callosal fibres degenerate; further lateralwards the degeneration is most distinct where they bend round the lateral angle of the lateral ventricle. It is impossible to discover well-defined degeneration in the centrum ovale. Peripherally from it, at the base of the gyrus ectolateralis, there is a loss of fibres which can be followed up to the cortex.

In the gyrus ectolateralis immediately anterior to the area striata, the subcortical white matter is less coloured than in the corresponding area of the normal animal. In the cortex itself the long, radiating fibres are greatly diminished in number. In the more posterior part of the cortex this degeneration is found only in the gyrus ectolateralis. Further frontally, a similar fibre diminution may be observed in the bend of the gyrus suprasylvius, which borders the gyrus ectolateralis. Frontal to the lesion of the corpus callosum, there is no degeneration, but I possess only Marchi preparations of this region after callosal lesions. The course taken by the degenerated cortico-petal fibres is illustrated by Sherrington and others; they spread in smaller numbers than one would expect, from the degenerated corpus callosum into the centrum ovale and can be traced right into the base of the lateral and dorsal gyri, but apparently only few extend in front of the sulcus cruciatus.

Only a few black granules can be seen in the deeper layers of the cortex; there is no question of being able to follow a typical Marchi degeneration of the radiary fibres high up into it. Portions of the cortex behind the operated region are entirely free from secondary degeneration.

Nissl preparations of cats operated upon in the above described manner show the following changes:—

Cell changes are found exclusively in those convolutions of the uninjured hemisphere, in which secondary fibre degeneration was

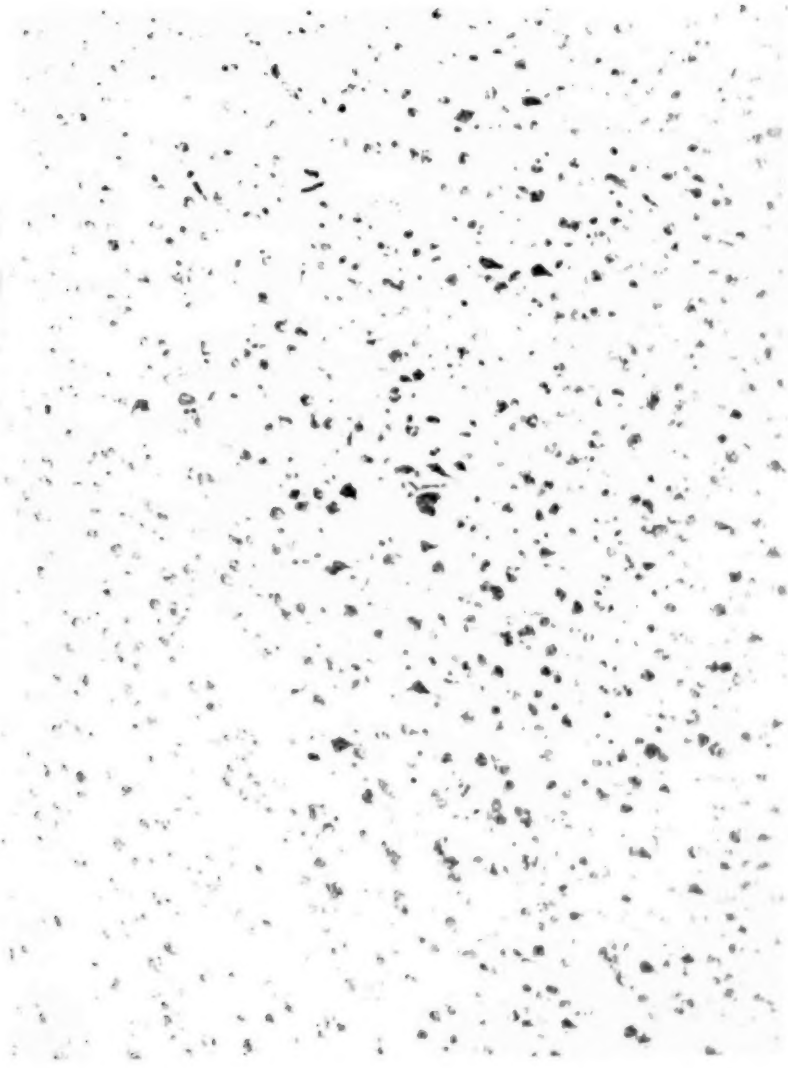

FIG. 8.—Cat: normal. Part of the cortex of the gyrus ectolateralis. Tolnidin blue.

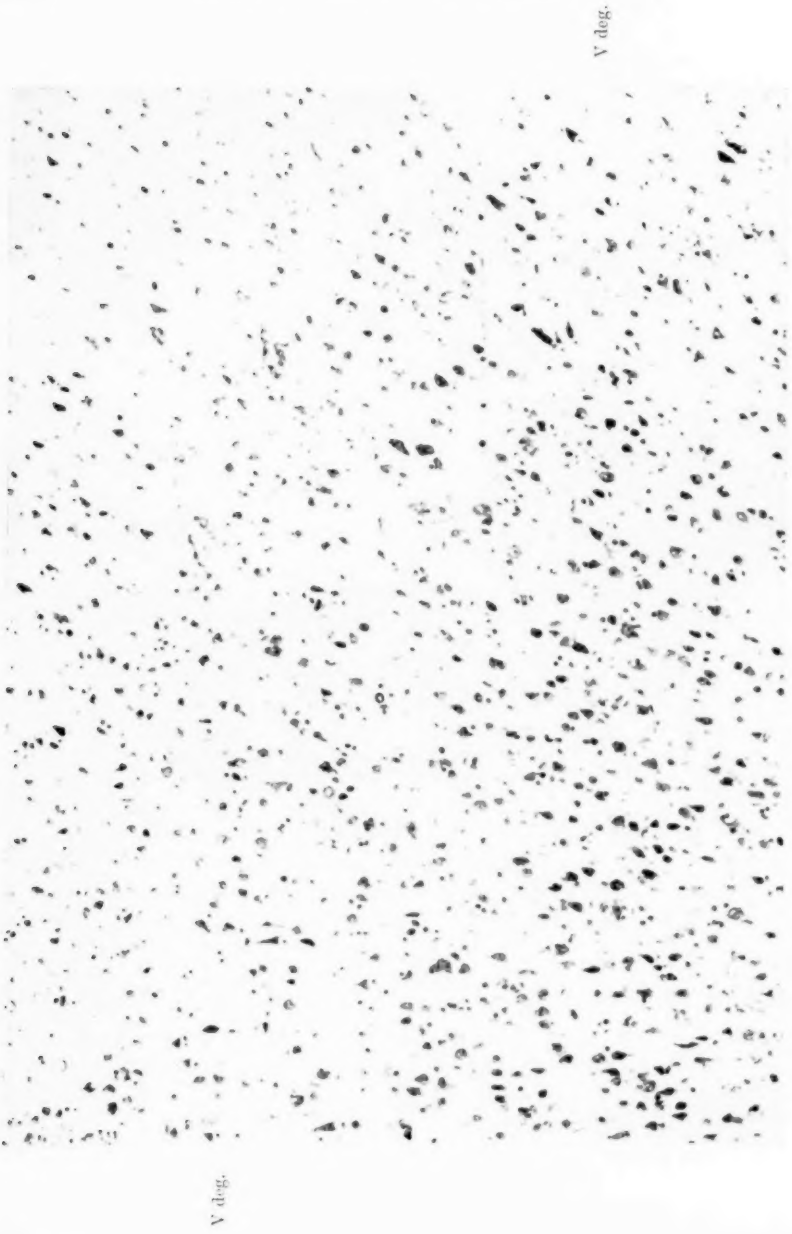

FIG. 9.—Cat: divisions of the posterior half of the corpus callosum. Part of the gyrus ectolateralis (corresponding with that in fig. 8).

discovered by the Weigert-Pal method. A pronounced loss of cells is very difficult to determine, but with strong magnification one finds, however, affected cells in the subgranular pyramidal layer, and possibly some in the sixth or polymorphic layer. The histological changes in these smaller elements are, however, exceedingly difficult to determine with positive certainty in material imbedded in paraffin, but as in the rabbit, there are no perceptible cell degenerations in upper cortical layers. Figs. 8 and 9, from the gyrus ectolateralis, illustrate these cell changes after sagittal section of the posterior half of the corpus callosum.

Pathological Cases.

In the introduction I alluded to the question whether cortical lesions cause secondary degeneration in the corpus callosum or not. That they do is admitted by most authors, as far as I am aware, except Kattwinkel. He examined, in Pierre Marie's laboratory in Paris, a great number of brains with very extensive cortical lesions and was never able to detect the slightest change in the corpus callosum. If the interpretation of this fact is difficult, the correctness of the observation can scarcely be doubted. It appears, however, to me that the large proportion of the fibres which have remained healthy is sufficient to account for the disappearance of all secondary callosal defect. On the other hand, Kattwinkel in his criticism of Dejerine's cases, is presumably right; the degeneration of the corpus callosum in these cases was not secondary, but primary. As a matter of fact, primary cortical softening cysts frequently occur accompanied by callosal lesions as Kattwinkel observed. One of my cases (No. 2) is a striking example of this.

A certain length of time is required for the total disappearance of secondary degenerated fibres of the corpus callosum. But it is evident that the duration of time between the onset of the lesion and death may be such that the degeneration of commissural fibres from the lesion may be clearly followed. Indeed, two of the following cases afforded this opportunity, as there were primary lesions of the corpus callosum and of the cortex.

Another method of determining the connexions of commissural fibres with certain cortical regions is possible when other fibre-systems in the immediate proximity are secondarily degenerated. In one case (No. 1) I was able to follow callosal radiations with certainty and to trace them later in preparations where all the fibre-systems were normal.

A.—Occipital Callosal Fibres.

Case 1 [52].—Hæmorrhage in the retrolenticular segment of the internal capsule, in the corpus geniculatum externum, and the frontal half of the sagittal strata of the occipital lobe. Secondary degeneration of the fasciculus longitudinalis inferior to its ending in the area striata in the occipital lobe.

Sections in the plane of the sulcus parieto-occipitalis were stained chiefly by the Pal method, with strong differentiation. The fibres of the corpus

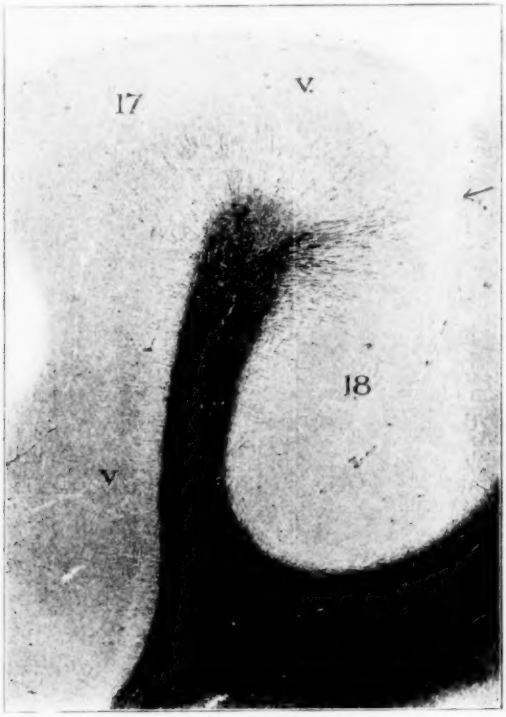

FIG. 10.—Case 1. ↓ Callosum fibres to field 18 (Brodmann) close to the Stria Vieq d'Azyr (V). Underlip of the sulcus calcarinus.

callosum from which the forceps and tapetum originate can be followed with absolute certainty from the forceps corporis callosi up to the occipital pole. It can be distinctly seen that fibre bundles separate gradually, both ventrally and dorsally, but the direction of the section makes it impossible to follow them into the different parts of the cortex at one level. But on the medio-ventral surface from the frontal end of the area striata to the occipital pole, fibres can be more or less clearly seen coming from the dorso-median or ventro-

median boundary of the tapetum or the forceps and passing to the upper and lower lips of the sulcus calcarinus. They terminate on the immediate boundary of the cortical field adjoining the area striata (field 18 of Brodmann; visuo-psychical area of Campbell, Mott, Bolton, and others). It may be stated with absolute certainty that not a single callosal fibre is connected with the calcarine cortex in the stricter sense of the term (area striata of Elliott Smith, field 17 of Brodmann). Fig. 10 shows the underlip of the sulcus calcarinus with the subcortical fibres of the lobus lingualis. These fibres are to a great extent degenerated, hence their pallor. One sees, however, a group of darkly stained fibres bending ventralwards from the white matter; these, which pass into the ventral cortex, can be followed continuously from the tapetum, 1·75 cm. from the occipital pole. This may also be seen in fig. 11. Both dorsally

FIG. 11.—Case 1. Continuous bundle from forceps corpus callosi (tapetum) to field 18. ca = sulcus calcarinus.

and ventrally in the regio calcarina these callosal fibres can be seen in connexion with the tapetum. The latter lies in the retrolenticular space, which is pale owing to total degeneration of the geniculo-cortical radiation. Owing to strong differentiation the Stria of Vicq d'Azyr is only faintly visible, but it is still distinguishable and of normal size.

Case 2.—Bilateral symmetrical softening of the cortex of the gyrus supramarginalis, gyrus angularis, a part of the lateral occipital convolutions extending down to the sagittal strata, and in the left hemisphere a softening in the calcarine region. The splenium is also softened, and there is secondary hæmorrhage in the posterior part of the corpus callosum.

During life there was serious disorder of speech (sensory aphasia), and visual disturbances, with partial mind-blindness.[1] The lesion in the right

[1] The clinical and macroscopical observations are described in v. Valkenburg, "Zur Kenntnis der gestörten Tiefenwahrnehmung," *Zeitschrift für Nervenheilkunde*, 1908, Bd. xxxiv. S. 322, and Kurze Erwiderung, &c., *Zeitschrift für Nervenheilkunde*, 1909, Bd. xxxv, S. 472.

hemisphere had caused no demonstrable left-sided hemianopsia, but microscopical investigation showed that in all probability a small scotoma had been overlooked, as there was a localized secondary loss of cells in the corpus geniculatum externum.

The softening in the corpus callosum was at first overlooked, and regarded as a secondary degeneration due to the approximately symmetrical cortical lesions; but closer scrutiny showed the primary nature of the lesion.

In addition to the splenium, the forceps and the tapetum of the right hemisphere were in part primarily, in part secondarily affected. In any case all the cortico-petal callosal fibres to the occipital lobe of the right hemisphere must have been destroyed, either primarily or secondarily. Consequently the callosal radiations to the cortex around the area striata could not be traced. Fig. 12, taken at about 2 cm. from the occipital pole, represents the underlip of

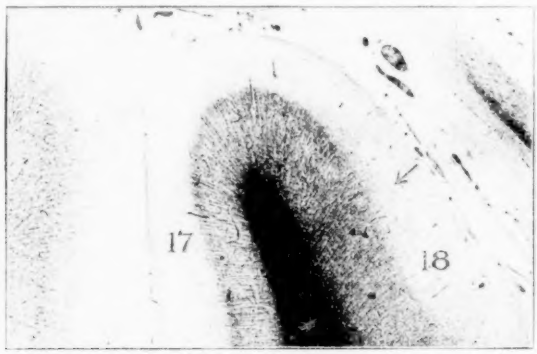

FIG. 12.—Case 2. Part of the regio calcarina (17); callosal radiation in field 18 absent, consequent on softening of the posterior part of the corpus callosum.

the sulcus calcarinus. Where the callosal radiations adjoining the Stria of Vicq d'Azyr are normally found, they cannot be identified.

These fibres can be, however, more or less distinctly seen in the cortex in certain sections, especially in field 18 and near the area striata, in either the upper or lower lip of the sulcus calcarinus. It is obvious that they are shorter; while those of Case 1 could be traced above the Stria of Vicq d'Azyr, those of Case 2 remained distinctly beneath it. It was only in the posterior occipital part of field 18 that fibres which correspond as regards their vertical distribution in the cortex, with those of Case 1 are found. These are especially seen near the upper lip of the sulcus calcarinus.

Case 3.—Anophthalmos congenitus. Slight reduction of the sagittal strata in the occipital lobe, moderate dilatation of the posterior horn of the ventricle, and the occipital lobe, particularly calcarine region, diminished in size. The cortex of field 17 normal; Stria of Vicq d'Azyr of normal size in proportion to the other cortical layers.

This case [55] has been selected because owing to the shortening of the Stria of Vicq d'Azyr the contrast between the relations of the callosal radiations to field 17 and field 18 can be admirably reproduced in one photograph.

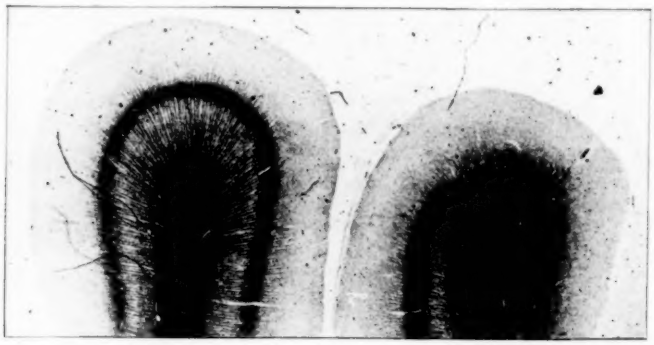

FIG. 13.—Anophthalmos. Lower and upper lips of the sulcus calcarinus; the first, in the area striata, without, the latter with callosal fibres.

FIG. 14.—Case 3. Anophthalmos; regio calcarina. ca = sulcus calcarinus. cc = callosal radiations in field 18.

On fig. 13, taken almost 2 cm. from the occipital pole, both the calcarine lips are seen. The stria does not reach the depth of the sulcus calcarinus, which therefore belongs to field 18. On the other hand, the apex of the convolution which adjoins the under lip (lobus lingualis) belongs to field 17. We see

long darkly stained fibres radiating from the white matter of the first convolution into the cortex, right up to the line of Vicq d'Azyr. The difference in calibre, as compared with the cortical radiation of the area striata, is very distinct. The surface of the under lip receives no callosal fibres; that this is not a peculiarity of the underlip, is proved by fig. 14. 2·5 cm. from the occipital pole a large callosal radiation may be seen in the wall of this convolution.

These fibres vary distinctly in length, the shorter ones only were found in Case 2. In this case of anophthalmos there exists a cuneo-lingual annectant gyrus by which the Stria of Vicq d'Azyr is interrupted in the sulcus calcarinus. In the walls of this deep convolution, which evidently belongs to field 18, the local callosal radiations can be easily found, as is shown by fig. 15.

FIG. 15.—Case 3. Anophthalmos; Stria Vicq d'Azyr interrupted by annectant gyrus. ca = sulcus calcarinus. c = callosal fibres in field 18.

Normal brain.—It remains to consider the question whether the callosal cortical radiations can be recognized in normal brains. If the pathological cases had not paved the way, it would have been absolutely impossible to trace the callosal fibres into the cortex with any degree of certainty, as it is quite impossible to establish, in a normal preparation, a continuity between the forceps and tapetum, and the cortical radiations. The fibre radiations found in the margins of field 17, close to the ends of the Stria of Vicq d'Azyr, must be partly callosal. Fig. 16, representing a part of a section taken at

1·2 cm. from the occipital pole, shows these fibres near the dorsal boundary of the area striata. They are equally present at its ventral margin, and may be seen in the whole of this region of the cortex with variable distinctness.

The callosal fibres of the occipital lobe do not all stand in connexion with this small field, which surrounds the area striata. In Case 1, it was distinctly seen that both ventral (lobus fusiformis) and dorsal and dorso-lateral (gyri occipitales) fibres stretch from the tapetum to the cortex.[1] It was, however, impossible to follow them there in

FIG. 16.—Normal brain. Upper lip of the sulcus calcarinus. Callosal fibres in field 18 between ↓ ↓.

continuity, and it is therefore doubtful whether in these parts of the cortex the fibres of thick calibre also come from the corpus callosum. We must confine ourselves to exact observations, and these lead us to conclude that no callosal fibres originate or end in the area striata, but that they are connected with the cortex immediately around it. There is every probability that the long fibres which can be followed to the plane of the Stria of Vicq d'Azyr are cortico-petal; this seems probable from our observations in Case 2, as here the splenium and forceps were degenerated, and consequently all fibres originating from

[1] I will not enter on the question of the composition of the tapetum; it is certain in any case that it is partially composed of callosal fibres.

the left and destined for the right hemisphere, which pass through the corpus callosum, must have undergone secondary degeneration. As shorter fibres persist where the long cortex rays have disappeared, it is evident that those should be considered as cortico-fugal projection and callosal fibres. As the softening in the corpus callosum was fairly recent (there were masses of "Körnchenzellen" and hæmatocytes present) it is possible that these had not yet undergone retrograde atrophy. The existence of a few long fibres in the same place, especially in the extreme occipital region, is another difficulty. If we deny the possibility that a few callosal fibres escaped, which is certainly not probable from our sections, we might suppose that we have here to do with collaterals of cortico-fugal callosal fibres which originated in other parts of the homolateral occipital lobe. This, however, is not proved. This supposition would afford an explanation of the existence of Sachs' and Vialet's association system, which I have already assumed in a former paper [52] to consist of callosal fibres.

Whether the commissural fibres, which have their origin and termination in the cortex close to the area striata, are connected with homotopical parts of the opposite hemisphere, cannot be decided from my cases with absolute certainty.

The fact that the regio calcarina, in the narrower sense of the word, is not connected commissurally with the opposite side, is both physiologically and clinically of the highest importance. Beevor's observations on the marmoset are now confirmed in the human brain for the first time. Dejerine's anatomical conclusions are consequently erroneous, and the physiologico-clinical considerations which are based on a direct connexion of the two visual spheres, are groundless. Beevor looks upon the persistency of the hemianopsia, produced by a cortical lesion, as due to the absence of a commissural connexion, so that one hemisphere cannot compensate loss of the other. It is evident that this argument is not valid; a lesion which destroys the visual cortex in the one hemisphere, would inevitably destroy all the cells from which callosal fibres could arise, so that a cortico-fugal commissural connexion would be impossible. This pathological fact cannot be quoted in proof of the absence of a callosal connexion between the areæ striatæ; on the contrary, all arguments which rest upon the presence of such a connexion must be discarded. The greater part of the arguments relate to the explanation of the different forms of mind-blindness, but attention may be directed to Wilbrand's interpretation, accepted recently by Lenz [25], of the fact that, in

hemianopsia of cortical origin, central vision generally remains intact. These writers assume that, frontally from the lesion, a connexion exists through the corpus callosum between the central visual tract in the affected hemisphere, and the calcarine region of the normal side. As they, together with Henschen, Flechsig, and many others, consider that the visual sphere is coincident with the area striata, such callosal fibres should consequently end in this area. The observations described above consequently disprove this hypothesis. We must henceforth consider the two primary end-stations of visual impulses in the cerebral cortex as, in a certain measure, independent of each other. It seems to me that, from a physiological point of view, this does not present any difficulty.

I fail to see any ground for assuming a connexion by which all impulses from one half of the visual field, after their arrival in the cortex, must be immediately placed in connexion with the centre for the other half of the visual field.

On the other hand, a commissural connexion is far more probable between the cortical centres from which eye movements can be evoked. Of late years Henschen [15] and others have assumed that the representation of the retina on the area striata should be so interpreted that in the upper lip of the sulcus calcarinus the two inferior quadrants of the visual field are represented, in the under lip the superior quadrants. According to Inouye's [17] theory, which appears to me extremely probable, there exists, moreover, a localization of the more central parts of the visual field (retina: fovea centralis) in more caudally situated regions of the area striata. The peripheral parts of the retina are, moreover, represented at the periphery of the area striata. It is stimuli from these peripheral portions of the retina that cause most eye movements of visual origin. It is true that the movements of both eyes are bilaterally co-ordinated from one hemisphere, and the probability is, therefore, greater that normally both hemispheres co-operate in their execution. On these physiological grounds it seems very probable that the callosal fibres connect homotopical areas, but this by no means excludes a heterotopical connexion. The experimental stimulation of the monkey's brain by Sherrington [45], who found foci for conjugated eye movements exactly along the sulcus calcarinus, supports this view. It appears to me indeed probable that Sherrington and Grünbaum stimulated chiefly this region. This is the more likely because Minkowski [32] also found that faradization of the area striata itself in dogs produced no effect, though he could excite eye movements from the second

"Urwindung" in its immediate proximity. The closely adjoining radiation of callosal fibres into the part of field 18 in the cat's and human brain, which is adjacent to the area striata, shows that the here incoming and outgoing commissural impulses must be strictly localized, as they are excited by relatively very circumscribed peripheral retinal impulses and are concerned in the production of accurate and precise movements of the eye-balls.

The dispute in regard to the localization of the fovea centralis in the cortex of the lobus occipitalis is still unsettled. From different clinical and pathologico-anatomical observations of late years, which cannot be discussed here, it seems to me that it is most probably represented in the posterior part of the area striata. In most cases this area extends round the occipital pole, to the lateral surface of the hemisphere.

If so, only a relatively small part of the extreme occipital region of this area is bounded by callosal radiations. The so-called "cortical macula" should lie further away from the commissural fibres. If this hypothesis, for which support may be found in the work of Niessl v. Mayendorf [38], Inouye [17], and others, should prove to be true, it would agree with these physiological considerations based on the distribution of the callosal radiation, as the only part of the retina from which reflex conjugate movements cannot be excited is the fovea centralis. That in mice and rabbits, which have no fovea centralis, the occipital lobe receives no callosal commissure-fibres, is no argument against my views. In these animals, which have a very small, if any, binocular visual field, the ocular movements are chiefly of vestibular origin, and do not result from visual impressions; the latter cause rather head- and neck-movements.

The following is another general argument to account for the total lack of a commissural connexion between the two areæ striatæ. It is in my opinion a general law in the structure of the central nervous system, that the anatomical structures concerned with different functions at different levels in their projection-course are similarly arranged. Undoubtedly there exists an extensive commissural connexion between the primary motor centres of the brain-stem, for instance, the oculomotor nuclei, but such has never been shown to exist between the primary optic centres of the mesencephalon and thalamencephalon. The posterior commissure, whose position between and frontal to the corpora quadrigemina anteriora or the lobi optici of the amammalia, might suggest that it is a commissure between them, has not been

shown to have this function. Sections of the posterior commissure in rabbits and cats never produce cell degeneration in the optic part of the anterior corpora quadrigemina, nor in the corpus geniculatum externum. The same is true for the lamina commissuralis tecti. As the sensory and motor representations of the eye-ball in the cerebral cortex are, in all probability, built on the same plan, though naturally modified in conformity with the more complicated functions of the fore-brain, it might be assumed that there exists a commissure between motor ocular centres, as indeed has been demonstrated in the monkey, and possibly a few other mammals. Sherrington [46] made its existence probable by obtaining conjugate ocular movements by stimulation of the splenium in monkeys. On the other hand, no connexion between the primary visual cortical centres through the corpus callosum would be expected. As I have shown, it is absent.

B.—Callosal Fibres of the Regio Rolandica.

Case 4.—Softening of the corpus callosum in the right hemisphere from the gyrus cinguli to the truncus corporis callosi. It commences caudally in the transverse plane that passes through the posterior part of the corpus geniculatum externum and extends frontally to the motor zone. In the left hemisphere a softening was present in the base of the gyrus supramarginalis, and some small scattered cysts in the cortex. Two sclerotic patches were found in the fasciculous longitudinalis inferior of the right hemisphere.

This case was an old woman suffering from arterio-sclerosis; nothing particular is known of her clinical symptoms. There is no history of apraxic disturbances, but presumably the patient's mental state made an examination on this point impossible.

The part of the callosum which lies in the frontal plane of the Rolandic region was destroyed by the softening, partly in the right hemisphere dorsal to the lateral ventricle, and partly in the median line; all commissural fibres in this part have been interrupted.

Fig. 17 shows the greatest extent of the softening. It represents a part of a section which contains the dorsal third of the gyrus centralis anterior. At this level only, the cyst extends to the central part of the lobulus paracentralis; elsewhere it remains below the sulcus calloso-marginalis. The corona radiata is practically unaffected, and in this level the left hemisphere was intact. A pale strip can be traced from the cortex of the gyrus centralis anterior towards the cyst; as it diminishes in width, and as the number of degenerated fibres it contains evidently decrease in number as it approaches the corpus callosum, it must have contained fibres which were not connected with this. It can be followed only to the motor cortex; its radiation into the cortex is better seen in fig. 18, which lies 1 cm. frontal to the occipital end of

the callosal cyst. The degeneration extends into the cortex and there spreads out fan-wise. The tangential fibres are as numerous as in the adjoining cortical regions, but the latter contain the ordinary radiary fibres, which are entirely absent in the affected area. The pale strip in the centrum ovale gradually becomes narrower towards the softening in the corpus callosum: a part of its fibres must undoubtedly have originated from this. Though no primary lesion exists in the cortex in this section, as is shown by the persist-

FIG. 17.—Case 4. M = softening. V = lateral ventricle. Degeneration strip from M to the cortex of the precentral gyrus.

ence of the horizontal fibres, there is a small vascular necrosis slightly frontal to it to which a part of the degeneration of the radiary fibres may be due. We may consequently consider the fan-shaped fibre loss as the result of both a cortico-fugal and cortico-petal degeneration: the first involved projection and commissural fibres, the second only the latter. The projection fibres belong

to the tractus cortico-spinalis, which we know originate in the fifth layer (lamina ganglionaris, Brodmann); all long cortical rays which have disappeared are therefore callosal fibres. I draw attention to the localized manner in which commissural bundles radiate into this cortical "motor" region.

FIG. 18.—Case 4. Precentral gyrus, upper part. Fan-shaped degeneration of radiary fibres between ↓ ↓.

In a section 2·2 mm. in front of fig. 18 the effect of the vascular lesion has disappeared; the degeneration strip in the centrum ovale and the white matter of this convolution is scarcely visible, though the callosal softening is unaltered. Only the longer cortical rays that reach the superradiary network have disappeared. From this we may conclude that the longer fibres radiating into cortex are cortico-petal callosal fibres. It is of course possible that commissural fibres also end more diffusely in these convolutions, as is shown in fig. 19. This represents the gyrus centralis anterior of the opposite side

FIG. 19.—Case 4. Precentral gyrus, middle part, left. The long intracortical callosal fibres (cortico-petal) are degenerated between ↓ ↓.

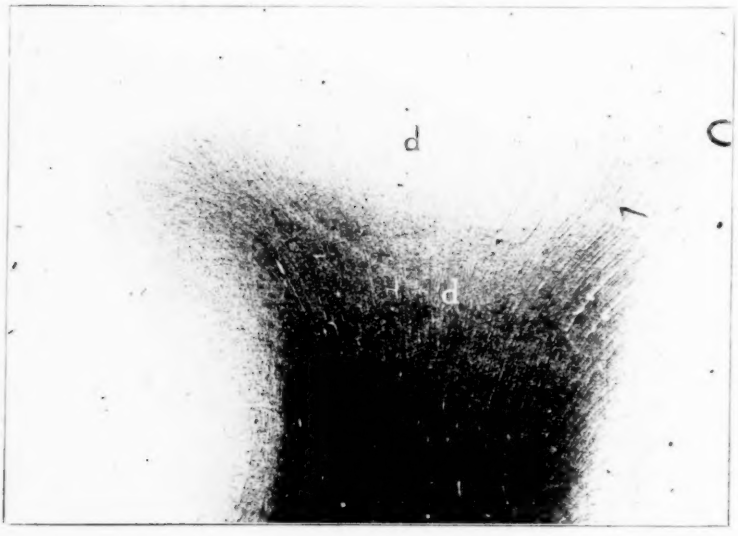

FIG. 20.—Case 4. Postcentral gyrus, right, 5 mm. behind the cyst. d d = secondary degenerations of infracortical and cortical callosal fibres.

1·5 mm. farther forward: the callosal lesion lies on the right. In the vertex of the convolution in which there is no sign of any primary lesion, it is clearly seen that many long radiary fibres have disappeared. It is true that the limits of the degeneration can be still defined, but it is evident that the loss gradually diminishes from its middle towards both sides.

A distinctly more diffuse character of fibre loss is seen on the other hand in the gyrus centralis posterior, which shows a diminution of the radiary fibres, but nowhere a localized degeneration.

A corresponding but far more striking loss of fibres is visible in the posterior central convolution of the right hemisphere, into which the callosal lesion extends. Fig. 20, a little more than $\frac{1}{2}$ cm. caudal to the commencement

FIG. 21. Case 5. Cortico-fugal degeneration, partly of callosal fibres from the upper part of the left precentral gyrus; * indicates a spot in the right precentral gyrus where secondarily callosal fibres are lost.

of the softening, shows no secondary degeneration in the fibres of the gyrus centralis posterior, except immediately below the cortex. It is evident that the secondarily degenerated fibres coming from the lesion, unite before radiating inwards. The entire dome of the convolution is marked by a paucity of radiary fibres, though they are nowhere entirely absent: towards the sulci, especially on the dorsal side (to the left on the figure), the increase of the radiation is very gradual.

Case 5.—A large softening in the left hemisphere, extending from the

occipital pole to the gyrus centralis posterior on the lateral convexity, and involving the dorso-lateral part of the sagittal strata. Scattered cortical vascular lesions, especially in the gyrus centralis anterior.

A softening in the anterior part of the gyrus fusiformis and lobus lingualis of the right hemisphere which also involves the ventral (horizontal) part of the sagittal strata.

There is very little known of the history of this patient: she was "demented" and too confused to be examined. The part of the brain which is of special interest is the Rolandic region, and the cortical lesions is in the left gyrus centralis anterior (fig. 21). In the anterior central convolution two small softenings are seen, from which two narrow strips can be followed to the

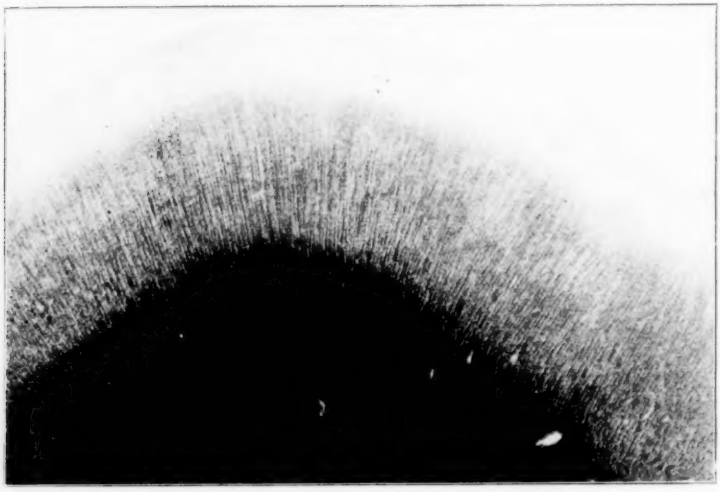

FIG. 22.—Case 5. Upper part of the right precentral gyrus. 1¼ cm. frontal to fig. 21. Loss of long cortico-petal callosal fibres between ↓ ↓.

dorso-lateral angle of the ventricle: during their course they become gradually smaller, especially as they pass through the corona radiata. Part of the degeneration can be followed into the supraventricular part of the corpus callosum, in which it speedily disappears. We have here a combined cortico-fugal fibre-degeneration of the projection and commissural systems. The other strips of degeneration, running more or less parallel, come from more frontally situated cortical lesions and follow a similar course. When we endeavour to follow these secondary degenerations into the right hemisphere, it is seen that, as in the corpus callosum, they cannot be identified in the centrum ovale; they can be recognized only at the termination of some of the subcortical fibre cones, and especially in the cortex. This absence of visible

continuity renders it impossible to state with certainty from which primary cortical lesions of the left hemisphere the lost radiary fibres in the right come. As the degenerated fibres come exclusively from the left gyrus centralis anterior, it may be concluded that this convolution is wholly responsible for them; it was chiefly its dorsal part, the "leg centre," that contained these softenings. Even in the slightly magnified figure a distinct loss of radiary fibres [at *] can be seen in the right lobus paracentralis, though the tangential fibres persist. Fig. 22 is a more strongly magnified photograph of the anterior part of the right gyrus centralis anterior, close to the dorsal margin, $1\frac{1}{4}$ cm. in front of fig. 21. There are several confluent softenings in the cortex of the corresponding areas in the left hemisphere, from which pale strips can be followed that partly disappear in the corpus callosum. The loss of cortical rays visible in the figure is in the exactly homologous area of the right side of the brain. There is a marked reduction of the long cortical rays, but the short ones are not definitely diminished in number. The boundaries of the region where the loss is seen are tolerably sharp on each side. As the cortical lesions in the Rolandic region of the left hemisphere are limited to the gyrus centralis anterior, and to particularly the "leg centre," this case may throw some light on the ending of those callosal fibres in the gyrus centralis posterior on the right side. In sections $7\frac{1}{2}$ mm. behind fig. 21, there is not a trace of any defect in the rays of the cortex of the dorsal part of the left gyrus centralis posterior. On the other hand, there is a distinct fibre loss in the homologous area of the right hemisphere, but it is not nearly as sharply defined as in the gyrus centralis anterior. The entire long cortical radiation has become much "thinner." The Baillarger layer is preserved as well as the tangential fibres. The limitation of the cortical lesions in the left hemisphere to the dorsal part of the gyrus centralis anterior is by no means absolute; it is, however, probable that those situated elsewhere have caused corresponding contra-lateral degenerations. In the transverse plane of the corpora mamillaria, about $\frac{1}{2}$ cm. frontal to the section from which fig. 22 is taken, we find a cyst in and under the cortex of the middle of the anterior central convolution, which is separated from the cortical lesions in the dorsal part of this convolution by normal brain tissues; both the cortex and the white matter ventral to it are intact. In the sections of the right hemisphere from this region we find a slight rarefaction of subcortical fibres due to secondary degeneration from the lesion in the left side, but a few degenerated cortical rays only are found in the homologous region on the right side; the degeneration passes further distalwards and reaches the cortex after having passed the base of the sulcus centralis. Finally, the diffuse degeneration in the subcortical substance of the convolution penetrates the cortex of the gyrus centralis posterior in about the same horizontal plane as the middle of the gyrus centralis anterior. Its termination lies in a sagittal direction about $1\frac{1}{2}$ cm. behind the origin of the degenerated commissural fibres. The cortical rays are diffusely diminished in number. Notwithstanding the numerous lesions in this half of the fore-brain, the fibre content of the posterior central convolution, if not normal, is

at least much greater than on the right side. As mentioned above, the ventral and dorsal parts of the convolution adjoining the softening, which occupied the middle part of the gyrus centralis anterior (the "arm centre"), were unaffected. On the other hand, the extreme dorsal part of the anterior central convolution ("leg centre") contained small foci of softening. The secondary degenerations resulting from these lesions in the cortex of the gyri centrales anterior and posterior on the right have been already described; they are apparently confined to the extreme dorsal parts of these convolutions. In the regions immediately ventral thereto, as in the cortex ventral to the middle of the two gyri centrales, the fibre loss is far less distinct or is entirely absent. One seems justified in seeking the cause for this difference in the extent of the cortical and subcortical softenings in the left anterior central gyrus.

FIG. 23.—Case 5. Middle part of the right postcentral gyrus. Diffuse degeneration of callosal fibres.

Further caudalwards where the left occipito-parietal lesion falls in the section, the conditions become too complicated to determine with certainty the cause of the degeneration of the cortical rays on the right side. It is, however, remarkable that in a section through the splenium the cortical rays in the right operculum are diffusely degenerated.

C.—Frontal Callosal Fibres.

Case 6.—Left hemisphere: necrotic cysts filled with fluid which isolated the cortex of the entire temporal lobe, the greater part of gyrus centralis posterior, and almost the whole of the parietal lobe, but the fibræ propriæ were almost everywhere preserved. Subcortical softenings in the ventral and most

dorsal parts of the gyrus centralis anterior, and in the base of F^1 and F^2. The white matter of F^3 (Broca's centre) was also involved. In the right hemisphere a single small softening in the temporal lobe (T. 3).

This case [53] was a woman of about 60 years of age, who had been ill for a number of years. Her symptoms were :—

Paresis of the right side of the face; helpless, hemiplegic gait, and Babinski's sign and foot-clonus on the right. Loss of kinæsthesia and astereognosis in the right hand; nowhere complete tactile anæsthesia; localization of touch in the right arm only slightly disturbed. No hemianopsia, but from investigation of the brain it is evident that there must have been a scotoma, as the left external geniculate body was partially degenerated.

Almost total aphasia, principally sensory, but she could still use a few words easily and properly; complete alexia and agraphia. She never used the right hand spontaneously; it was, however, not paralysed as even delicate movements of the fingers were possible.

Motor apraxia of the right arm, and of the tongue and face. The apraxic disturbances in the left arm were extremely slight; they were generally only evident when two-handed movements were attempted.

This case afforded very little fresh information on the localization of apraxia. Both the gyrus supramarginalis (Liepmann) and a part of the three frontal convolutions immediately in front of the motor zone (Hartmann) were softened subcortically; and the greater part of the white matter of the gyrus centralis posterior and the lobus parietalis were destroyed. The aphasia was due to the temporal lesions, which extended to F^3 along the insula.

The corpus callosum was nowhere directly affected, but it was much reduced, especially in its centro-parietal part; its vertical measurement was not more than 1 mm. No secondary degeneration could be detected in it; but the considerable shrinkage it had undergone was certainly a result of the enormous loss of substance in the left hemisphere. The destruction of this was so extensive that it is impossible to determine definitely a connexion between the affected callosal radiations in the right hemisphere and special regions of the left cortex.

I will rather, therefore, use this case to demonstrate a few bundles, which from their immediate proximity to the corpus callosum are of importance in the study of the latter.

Two fibre-systems must be considered :—

(1) The fasciculus subcallosus (Muratoff [36]), fasciculus nuclei caudati (Sachs [43]), or fasciculus longitudinalis medialis (Anton u. Zingerle [1]).

It is usually held that this system has nothing to do directly with the corpus callosum. Muratoff showed that certain of its fibres degenerate in consequence of lesions of the regio sigmoidea in dogs. Anton u. Zingerle demonstrated connexions with the capsula externa and stated

that it has probably numerous connexions with the cortex of the fronto-parietal region and with the basal ganglia.

My case enabled me to confirm this latter view, as owing to the degeneration of a large part of the white matter of different convolutions, the remaining fibres could often be followed over a considerable extent in one section. Fig. 24 shows a part of a frontal section through both hemispheres; only the most ventral part of the left gyrus centralis anterior and the upper and the middle portions of the gyrus

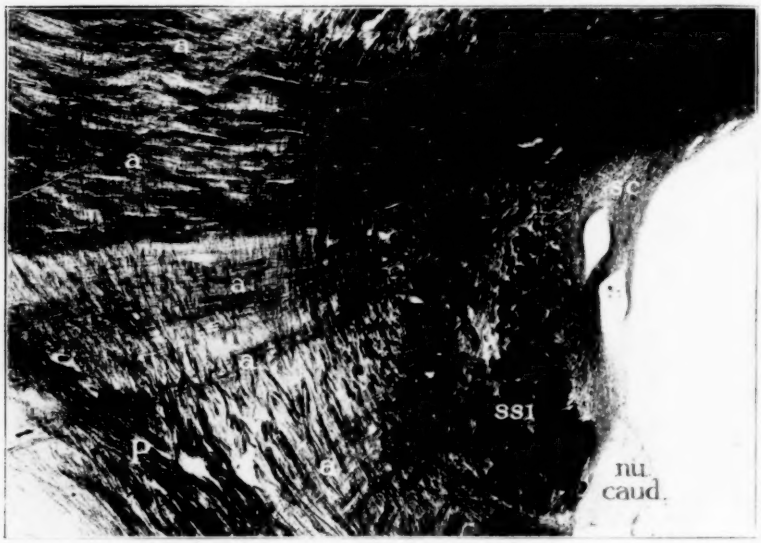

FIG. 24.—Case 6. a = fibres from cortex to fasciculus subcallosus (partly degenerated and to corpus callosum. sc = fasciculus subcallosus. ssi = stratum sagittale internum. P = pyramidal tract.

frontalis are situated in this plane. A great portion of the corona radiata is degenerated, but projection-fibres from the gyrus centralis anterior (facial and tongue centres) persist. These pass transversely through the dorsal part of the external capsule, and dorsally to the nucleus lentiformis to the lateral part of the internal capsule.

Separated from these by a broad pale zone the medial fibres of the corona radiata pass to medio-dorsal portions of the frontal gyri. Both bundles are traversed vertically by finer fibres, but the latter are partially degenerated, and only certain bundles are preserved. They

can be followed from the external capsule and from the lower part of the gyrus centralis anterior to the fasciculus subcallosus, where they terminate abruptly. In the most dorsal part of the figure one sees better preserved fibres coming in exactly the same manner from F^2; these can be also partly followed to the fasciculus subcallosus, partly to the lateral region of the corpus callosum, and a similar connexion exists with F^1. In fig. 25, from a section 1·2 cm. in front of the former one, the fasciculus subcallosus is greatly increased in volume.

FIG. 25.—Case 6. a = fibres from cortex to fasciculus subcallosus (partly degenerated) and to corpus callosum. sc = fasciculus subcallosus. ssi = stratum sagittale internum. d = degenerated part of fasciculus subcallosus.

The lateral part of F^3 is partially degenerated in consequence of the subcortical cyst in F^3 and F^2, and a pale strip can be traced from it to the fasciculus subcallosus.

Similar connexions between all the fronto-parietal convolutions and the fasciculus subcallosus can be seen further posteriorly where this latter extends, behind the nucleus caudatus, into the "substance sub-ependymaire" (Dejerine). The same connexions, less in number, exist between cortex and the fibre mass along the posterior horn (part of the tapetum).

The fasciculus subcallosus in these and more frontal sections is much

larger than it appears. The coarser and more darkly stained fibres in the neighbourhood of the lateral ventricle surround it and largely hide it from view. The fibres of the corpus callosum lie dorsal to the ventricle, but are separated from it by the fibres of a peculiar bundle which we must now consider.

(2) Fasciculus occipito-frontalis; stratum sagittale internum (Anton u. Zingerle), or reticuliertes Stabkranzfeld (Sachs). This bundle appears lateral to the ventricle at the level of the retrolenticular part of the internal capsule, immediately lateral of the tail of the nucleus caudatus. It is undoubtedly in connexion with the internal capsule as Anton u. Zingerle, Sachs, and others rightly maintain. Frontally the bundle increases considerably owing to accession of fibres from the median part of the capsula interna, as figs. 24 and 25 clearly show. From the dorsal margin of the bundle fibres which pass off in a dorsal direction may be followed to the lateral part of the corpus callosum. Wernicke therefore came to the conclusion that these fibres pass from the capsula interna into the corpus callosum, and from the study of different preparations, both normal and pathological, I have more than once been inclined to accept this view. But the view of Anton u. Zingerle is certainly correct, as, especially in more frontally situated sections (fig. 25), the fibres can be traced from the tip of the bundle, through the callosal radiation, towards the dorso-median gyri. From the study of Case 4, in which this bundle was to some extent atrophied, I consider that it radiates into the gyrus frontalis superior and probably to the gyrus calloso-marginalis.

A case in which the corpus callosum, except for a very small part of the splenium, was destroyed during the first year of life, confirmed this supposition [52]. In addition to the corpus callosum, however, the entire mesial wall of the frontal lobe and the paracentral lobule were destroyed. As the stratum sagittale internum persisted, though considerably diminished, it must necessarily be also connected with the more dorsal portions of the frontal lobe. My preparations give the impression that this bundle forms the projection-radiation of the dorsal part of the lateral nucleus of the thalamus. The radiation terminates for the greater part in front of the lesion, which extended to the base of the upper and middle frontal convolutions; Case 6, in which the bundle was equally well preserved on both sides, shows this clearly. In summarizing our observation on the callosal radiations of the regio Rolandica, and the frontal lobe, I must first emphasize that this investigation has by no means solved all the questions. In my anatomical conclusions I will simply confine myself to the facts personally observed.

Callosal fibres can be far less distinctly followed into the cortex in the regio Rolandica than in some parts of the occipital lobe. In this region there is a well-defined isolated system (forceps-tapetum), and with a favourable plane of section and proper staining the fibres can be continuously followed into field 18, and possibly elsewhere. But the fibres of the body of the corpus callosum cannot be traced directly to the cortex in transverse sections: part of these turn ventralwards round the lateral ventricle, mesial to the corona radiata, but the greater part pass dorso-lateralwards and in an oblique sagittal direction. I can confirm the description of Anton u. Zingerle [1]. Moreover the ending in the cortex of the fibres that ascend vertically from the lateral part of the corpus callosum, is far more diffuse than in the occipital lobe.

The cortical lesions in Case 5, particularly those in the anterior central convolution, and the secondary fibre-degeneration resulting therefrom, prove that cortico-fugal callosal fibres run in compact bundles between the cortex and the lateral portion of the corpus callosum; they run almost vertically to it. Further, as Case 6 shows, there is a great danger of confusing the association fibres of the fasciculus subcallosus with true callosal elements; this error is the more possible, as the fasciculus subcallosus is covered by callosal fibres over a greater area than one would believe from normal preparations. In this respect the sections of Case 4 are important. Indeed, while the corpus callosum was completely destroyed in the Rolandic region of the right hemisphere, the fasciculus subcallosus was practically intact. Bundles which could be followed, however, from the cortex to the cyst were evidently destined for the corpus callosum. These degenerations were remarkably similar to those in Case 5; this was in consequence of the small cortical lesions which produced a corresponding fibre loss. There is, however, a distinct difference; in Case 4 the fibre loss extends further than the cortical disturbance, and, as fig. 18 so strikingly shows, the degenerated radiary fibres occupied a fan-shaped area towards the cortex. The conclusion one would easily draw from a study of the preparation from which fig. 18 is taken, is that the degenerated fan consists of degenerated cortico-petal callosal fibres, resulting from the callosal softening. The fact that a cortico-fugal callosal degeneration (Case 5) certainly produces exactly the same fibre loss in the centrum ovale must, however, act as a deterrent from drawing such a conclusion. Moreover, a further investigation of the series will prevent us from doing so, a cortical lesion being found in the immediate proximity. This justifies the conclusion that the same part of the gyrus centralis anterior,

from which compact fibre bundles arise, also receives cortico-petal commissural elements.

When a lesion which does not involve the cortex produces an isolated commissural degeneration, the disappearance of the cortico-petal callosal fibres alone is not sufficient to cause a well-defined tract of degeneration up to the cortex. It necessarily follows that the callosal radiation must be more or less diffuse. Case 4 (fig. 18) proves, however, that in the gyrus centralis anterior this diffuse character is not absolute, as callosal fibres from the one hemisphere end where other callosal fibres arise. The latter, however, are fewer in number; it is evident that the cortico-fugal degeneration nowhere consists exclusively of commissural fibres. It thus follows that besides a homotopical connexion, which must certainly be admitted, there is also a heterotopical one. I cannot make out in what relation the termination of these fibres stand to the place of origin of the callosal fibres. It was only in the gyrus centralis anterior that I could with certainty determine the close correspondence in their origin and termination. The illustrations of cortex of the undamaged hemisphere in Cases 4 and 5 show this also. Moreover, the preservation of the short cortico-fugal cortical radiations, and the disappearance of the longer cortico-petal rays, are here visible. It is evident that the cortical fibre degeneration due to the callosal lesions is equally diffuse in the gyrus centralis posterior, while the local loss of fibres is less circumscribed than in the gyrus centralis anterior. I cannot determine with certainty the origin of callosal fibres in the gyrus centralis posterior. In the cases with cortical lesions, such as those described in gyrus centralis anterior, I never saw such distinct fascicular degenerations.

I believe I may be justified in stating that in the *posterior central convolution* :—

(1) The relation of the origin and termination of the callosal fibres is not definitely local.

(2) The ending of these fibres is relatively diffuse.

(3) Fibres end here which come from the contra-lateral gyrus centralis anterior, and to some extent at least the origin and termination both in front and behind the sulcus centralis are situated in the same horizontal level.

On the other hand, the *anterior central convolutions* are :—

(1) Connected *homotopically*, in the sense that the origin of cortico-fugal fibres is more or less surrounded by a radiation of fibres from the homologous spot on the opposite side; it is doubtful if there

exists a heterotopical connexion between the gyri centrales anteriores; I have no argument in favour of it.

(2) They are connected with the contra-lateral gyrus centralis posterior in the manner described above. The fibres which form this heterotopical connexion are apparently far more numerous.

It is possible that the relations of the callosal rays in the prefrontal gyri can be better followed than those of the centro-parietal region, owing to the more sagittal course of the commissural fibres around the cornu anterius, resembling in this respect the forceps and tapetum in the occipital lobe. I have, however, not been able to collect such positive information with regard to the frontal lobe as Case 1 afforded of the relations of the commissural fibres to Brodmann's field 18. It was only the region of the base of the third frontal convolution in Case 6 which could bring light to bear on this. In the first place it results from these preparations, that, even when there is not a primary callosal lesion, the great commissure decreases very considerably in volume owing to the destruction of a part of the centrum ovale and of the centro-parietal region, as indeed might be expected. It is very difficult to follow in continuity fibres from the frontal and temporal convolutions in the corpus callosum, but it is certain that they have a very similar course to those that definitely run medialwards into the complex of the fasciculus subcallosus. In Case 6 it is not possible to determine whether in certain places these radiary fibres pass into the corpus callosum or into the fasciculus subcallosus. In the dorsal part of figs. 24 and 25 fibres to both destinations may be seen. It is very likely that the termination of commissural fibres is diffuse on the opposite side. There is, however, such a doubtful loss of cortical fibres in the uninjured hemisphere that one must suppose that here, even to a greater degree than in the Rolandic region, the commissure does not connect homologous parts. More than one preparation led me to suppose that a part of the corpus callosum serves to connect the neostriata on each side, that is the nucleus caudatus and putamen nuclei lentiformis. But I have not been able to find cell degeneration of these ganglia which would be a convincing proof of this. In analogy with the archistriatal commissure which connects the nuclei amygdalæ, and a possible commissure between the palæostriata in Meynert's commissure, such a connexion of the phylogenetically most recent parts of the striatum would not be improbable. In any case there is a considerable number of fibres in the corpus callosum which unquestionably passes from the one hemisphere to the other, the origin and ending of which we do not

know with any degree of certainty. On these grounds the statement that the corpus callosum simply connects the cortex of both sides, either homotopically or heterotopically, or in both ways, must be abandoned.

The height to which the cortico-petal callosal fibres ascend in the cortex is indicated by the preparations from which figs. 19, 20, 22, 23, have been taken; in these either the short fibres are intact, or smaller proportions have disappeared than of the long ones which reach into and above Brodmann's layer IV.

I have been unable to determine with certainty from these investigations on human brains from which cells of the cortex, or from which layers, callosal fibres arise. It is certain that the giganto-pyramids of field 4 (Brodmann), in the cases where the gyrus centralis anterior was completely separated from the centro-parietal callosal radiation, have not suffered appreciably. I have had no opportunity of investigating the remaining cortical areas in cases of isolated callosal lesions with satisfactory cell-staining methods.

The cell changes discovered in the deeper cell layers in the experimental observations on the cat, rabbit and mouse, were possibly only temporary.

Various remarks have been made already concerning the physiological significance of the callosal fibres of the "parastrial" part of field 18. An attempt has been made to explain the fact that the primary visual cortex is not commissurally connected with the opposite side, while the surrounding region, which is closely associated with eye-movements, has commissural fibres. In the remaining portions of the occipital cortex the callosal ending appears to be diffuse. A relatively circumscribed termination of callosal fibres occurs in the Rolandic zone, from which compact cortico-fugal bundles—consisting of commissural and projection fibres (including the pyramidal tract)—arise. According to Mott, a direct influence of corresponding points of the "motor" cortex on each other appears to be certain, while the connexion between the gyrus centralis anterior of the one and the gyrus centralis posterior of the other side seems to be more diffuse. As already stated, the origin and ending of this connexion lies in about the same horizontal plane, both in front and behind the fissure of Rolando.

The posterior central convolution is above all a primary cortical sensory centre, and contributes in large measure to the building up and the regulation of the movements which are innervated from the gyrus centralis anterior; these motor impulses descend from the giganto-pyramids of the fifth cortical layer. Both homotopical commissural

impulses from the contra-lateral anterior central convolution to the superficial layers of this motor field, and the heterotopical impulses from the same region, to the adjoining part of the posterior central convolution, may also contribute to the elaboration of the motor impulse.

The inability to follow the commissural connexions of the frontal lobes, even though they probably exist, adds to our ignorance of the functional significance of these regions and renders physiological conclusions on this part of the corpus callosum impossible.

A few clinical remarks were made in the introduction on the pathology of the corpus callosum. It is remarkable that of all the symptoms described in cases of callosal lesions very few may be ascribed, with any degree of certainty, to destruction of the commissural connexions. Perfectly isolated callosal lesions rarely, if ever, occur, and the total absence of this great commissure does not *necessarily* cause any typical symptom. I therefore neglect many intrinsically interesting communications of cases in which, in addition to other disturbances, the corpus callosum was absent, and where possibly a special symptom might be ascribed to this. It must be admitted that the symptomatology is very variable. Practically only those cases come under consideration where either an isolated, or more or less local, callosal softening existed, or in which by a softening in one hemisphere, a function was disturbed, which is not under the control of that hemisphere alone. Such disturbance, when remote influence by a tumour, &c., may be excluded, can only be explained through the commissural fibres.

In the first place my investigation offers an anatomical explanation of the well-known fact that in cases of cortical epilepsy the excitation of a motor centre in the affected hemisphere, can cross through the corpus callosum to the homologous centre in the healthy hemisphere. If the progression of the convulsions from the one side to the other is not accurately homotopical, as is indeed often the case, it may be assumed that the excitation of the centre first affected was so strong that the irritation spread directly from here to the homologous region of the opposite hemisphere.

Indirect apraxia (apraxia callosa) of the left extremities which Liepmann has described, is assumed to be due to a lesion of the commissural connexion between the left and right sensorio-motor centres. This view, put forward by Liepmann, is closely connected with his statement that the left sensorio-motor centres have a primary

rôle in evoking more complicated actions in general; even the movements necessary for given action of the left limbs are innervated from the right hemisphere. The result of my anatomical investigations, that there exists a connexion between the gyrus centralis anterior and the two contra-lateral central convolutions, may assist in the explanation of the fact that this indirect apraxia itself can be considered as a "cortical" disturbance ("gliedkinetische, innervatorische Apraxie"). The movements of the left arm are then not disturbed in consequence of a deficient formulation of the "psychic plan," nor by the ineffective transmission of the "plan" to the region, whence the execution takes place finally, but by the inadequate execution of the action itself, as this depends on the adequacy of the immediately preceding intra-cortical activity; but this must not be confused with the regulating impulses from the immediate proximity, the disturbance of which produces cortical ataxia. In Case 6 only two-handed movements were disturbed, not only because these needed the co-operation of the apraxic right hand, but because the functions of the left hand were primarily affected. All remaining actions of the left hand, as far as they could be examined in the aphasic patient, were quite normal.

In addition to the complete apraxia, there was a strong disinclination to make any movement of the right hand or arm. Whether its innervation was affected by the extensive centro-parietal, or by the frontal softening, as Foerster [8] and others seem to believe possible, it is certain that the initiative of the left arm and hand was not lessened by these large lesions. There can be, in any case, no question of a unilateral "eupraxic-centre."

Finally, there is the question as to the causes of mind-blindness. A lesion of the posterior part of the corpus callosum is generally considered, at least partly, responsible for this. If this assumes that it is due to the commissural connexion between two primary visual fields (areæ striatæ) being disturbed, the view is untenable, as it is an anatomical fact that no such connexion exists. If the chief cause of mind-blindness is to be sought in a lesion of the callosal fibres, it must be of those that connect other parts of the two occipital lobes, and it is certain that fields 18 and 19 (Brodmann) receive and give rise to parastrial radiations. These regions of the cortex comprise the "visuo-psychic area" of the English authors (Bolton, Mott, Campbell). It is certain that these fields co-operate with the area striata in the higher visual functions. They are, moreover, phylogenetically more

recent than field 17, and increase relatively in the higher mammals. Parallel with this the occipital callosal fibres become more abundant. The exactness of the hypothesis of Niessl v. Mayendorf, that in visual function the left hemisphere predominates over the right, and localized softenings of the pole and ventral part of the occipital lobe ("left macula centre") may cause mind-blindness, can be determined only by fuller clinical and anatomical investigations.

One will then have to reckon with the fact that the area striata has no commissural connexions.

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SENSORY CHANGES IN FRIEDREICH'S DISEASE.

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THE sensory changes in Friedreich's disease have been studied by several observers. Noïca, in two cases of the disease that he examined carefully, found very considerable loss to different forms of sensibility. Egger, in his investigations of "osseous sensibility," considered that this is regularly affected in Friedreich's disease. Other investigators have from time to time reported cases in which a certain amount of sensory loss was present, and cases indeed with some sensory loss have been mentioned incidentally from the time of the early differentiation of the disease from tabes dorsalis, and its occurrence is referred to in most neurological text-books.

The classical description of the disease, however, while admitting that loss to some or all forms of sensation may occur, regards it as altogether an unusual and exceptional feature, notwithstanding the fact that one of the great sensory paths of the cord is the chief site of the pathological changes that are present in the disease. A series of systematic observations, therefore, on a considerable number of cases of Friedreich's disease would seem justified, in order to see how far the classical description of the disease holds in the light of our present knowledge concerning the different forms of sensibility.

The chief aim, however, in undertaking this work has been the important question of sensory conduction in the cord, as the more recent work of Petrén, Rothmann, Head and his collaborators, and other investigators make it probable that impulses underlying the sense of position and appreciation of passive movement, the recognition of two compass-points simultaneously applied to the surface of the body, the appreciation of vibration, and the recognition of size, shape, form, and weight, and possibly of roughness and texture, are conveyed through the dorsal columns, tracts of which there is systematic degeneration in Friedreich's disease.

Most investigators now agree with the view that the dorsal columns

furnish the principal pathway in the cord for the conduction of the impulses that subserve muscle-sense, meaning by that term chiefly the sense of position in space and the recognition of passive movement. Petrén concludes from his examination of cases of stab wounds involving the spinal cord that these impulses pass up the cord uncrossed in the dorsal columns and in the dorsal spino-cerebellar tracts, but the view of Head and Thompson, based on their investigation of the grouping of sensory elements in Brown-Séquard lesions, that the dorsal columns subserve the conduction of the impulses underlying the recognition of position and movement that pass to consciousness, while the spino-cerebellar tract is concerned with those impulses that are responsible for the unconscious maintenance of equilibrium, seems likely to be the more correct, and Thompson has adduced later clinical and pathological evidence from a case of Combined Degeneration to show that the sense of position and recognition of passive movement may be grossly affected by a lesion limited to the long fibres of the dorsal columns.

Head and Thompson have shown also that the recognition of compass-points simultaneously applied is dissociated in the cord from tactile sensibility, and passes up uncrossed in the dorsal columns, while Bing has brought evidence that the impulses that subserve the appreciation of vibration also pass up the homolateral side of the cord, and therefore must be conducted by the dorsal columns.

The investigations of Head and Holmes on Brown-Séquard lesions, cited in their paper, go to show that not only do the knowledge of position and passive movement, the recognition of two points, and the appreciation of vibration depend on the integrity of the dorsal columns, but that the recognition of size, shape, form, and weight, and the appreciation of consistence and texture are affected in common with these other elements of sensibility, and the impulses which underlie them would seem, therefore, also to be conducted by the dorsal tracts. Thompson also, in his case, noted that the recognition of weight was grossly affected, as well as the appreciation of position, movement and double contacts. I have had the opportunity, moreover, of seeing recently another, as yet unpublished, case of cervical Brown-Séquard lesion, studied by Dr. Holmes and Dr. Head, which goes to confirm the view that the impulses which underlie recognition of size, shape, form, weight, consistence and texture, as well as the appreciation of position, movement, simultaneous contacts and vibration, are conducted through the homolateral side of the cord.

The impulses of light touch and pressure-touch are, according to

most of these observers, associated together in the cord. These impulses are conducted partly by an uncrossed path in the dorsal columns, mostly by a crossed path in the lateral columns (Petrén), or in the ventral columns (Rothmann). The localization of tactile sensibility is associated with touch and is mainly in the crossed pathway.

All impulses of whatever kind that are painful, all heat impulses and all cold, cross almost at once after a relay in the dorsal horns, and pass up the cord in the opposite lateral column, though possibly some of them pass without crossing by the lateral column of the same side.

Systemic degenerations of the dorsal columns are not numerous. Tabes dorsalis, it is generally recognized, is, at least predominantly, a disease of the dorsal roots. In Combined Degeneration the process is probably not a true system degeneration but a funicular myelitis (Nonne). In Friedreich's disease, however, we have a condition which is usually regarded as essentially a systemic degeneration of the dorsal columns, even although the pathological changes are not limited to them.

The changes in the dorsal column tracts are the most constant and most pronounced feature of the pathological anatomy of the disease, and are present in all cases. In the sacral and lumbar regions these tracts may be almost entirely degenerated, but higher in the cord the degeneration in the column as a whole is not so marked. In the dorsal and cervical regions, the root-entry zone seems considerably less affected than the rest of the column; and the cornu-commissural zone, the areas immediately next the grey matter of the dorsal horns, and Lissauer's tract may be scarcely at all affected. The degeneration in the other parts of the column, however, remains very severe throughout the whole cord. The long and medium fibres of the dorsal columns are therefore the ones chiefly affected, and the affection of these may be so intense that scarcely a fibre may remain visible in cross-section.

In the other tracts involved in the disease, the pyramidal and the spino-cerebellar, the degenerative changes are rarely so great as in the dorsal columns. The affection of the pyramidal tracts is most intense in the sacral and lumbar regions and diminishes as we pass up the cord, though in some cases it may be traced as far the pons or the lower part of the crus. The degeneration in the spino-cerebellar tracts, on the other hand, increases in extent and degree, from below upwards and becomes most pronounced in the higher cervical segments.

As contrasted with the great affection of the fibres in these different tracts, and especially in the dorsal columns, the changes in the cells are not so frequent or so pronounced except, perhaps, in Clarke's column. In some cases the spinal ganglion-cells are slightly atrophied and the

dorsal spinal roots and even the peripheral nerves may be involved. There is, however, no sufficient reason to consider that the affection of the dorsal columns is secondary to a primary degeneration of the ganglion-cells or of the dorsal roots, for the changes in the roots are not nearly so definite, so frequent, or so intense as in the dorsal columns, and the affection of the ganglion-cells is slight and inconstant.

The widespread nature of the pathological changes in this disease and its variable incidence on different systems of fibres in the cord are in harmony with the view that it is a true systemic degeneration of the long spinal tracts, and especially of the dorsal column system. But even if the degeneration in the dorsal columns be regarded, not as a primary systemic one, but as due to an elective or chance degeneration in the dorsal roots, the existence of profound changes in these columns is by far the most outstanding feature of the pathology, and we should expect, therefore, to find in Friedreich's disease those forms of sensibility disturbed which have been assigned to the dorsal columns, and disturbed in proportion to the intensity of the dorsal column affection.

For the purpose of investigating this, I have examined systematically twenty cases of Friedreich's disease. These were obtained from the practice of the National Hospital, Queen Square, and I must here express my indebtedness to the medical staff for permission to publish the results of my examination. To Dr. Gordon Holmes I am very specially indebted also, for constant help and advice throughout the whole investigation. All the patients examined presented the usual signs of Friedreich's disease, the skeletal deformities, the absent deep reflexes, the extensor plantar responses, the nystagmus, and the ataxia so characteristic of the disease.

The methods used in examining these patients were mainly those employed by Head and Holmes in their work on sensory changes in cerebral lesions, in as far as these were applicable. They had to be modified somewhat, because the symptoms in Friedreich's disease were of course bilateral, and, therefore, there was no sound side which could be used as a standard of comparison to estimate the amount of loss present as in Head and Holmes' work, where the disturbance was unilateral.

Tactile sensibility was tested by means of light touches with jeweller's cotton-wool. It was not considered necessary or advisable to employ more elaborate methods, or to attempt to obtain thresholds by means of von Frey's hairs. It was found that just as satisfactory

results could be got by means of the light cotton-wool as by von Frey's hairs in the cases in which both were used and the results compared.

Pressure-touch was examined by means of contacts with the observer's finger or other blunt object. The localization of tactile sensibility was tested usually by Head and Holmes' modification of Henri's method. Cutaneous sensibility to pain was examined by means of a pin-prick, and the appreciation of differences of temperature by means of tubes of hot and cold water of moderate degrees of temperature. Pressure-pain was tested by noting the amount of pressure on the subcutaneous structures necessary to produce discomfort. Cattell's algometer was used in many instances to test it, but was found so unsuitable for the character of the cases studied that its use was abandoned.

The sense of posture was tested in the usual way by making the patient indicate by description or by imitation with the homologous limb the position in which any segment of the limb that was being examined was placed; or by making him point with one index-finger to the position in space of some fixed point, such as the tip of the opposite index-finger, or the heel or the toe of the limb under examination. The latter method was naturally untrustworthy in cases in which there was either much ataxia or much loss of the sense of posture in the arms.

The appreciation of passive movement was examined in the ordinary way also by moving any segment of a limb slowly and uniformly through an angle sufficient to allow the patient to appreciate the movement and recognize its direction. It is, of course, important that the necessary pressure made by the examiner in holding the limb should be varied as little as possible, lest the patient should become aware of the movement by adventitious sensations. Where the loss is considerable this rough clinical method is sufficient, though, of course, due weight must be given to the intelligence of the patient, to the readiness with which he can respond, and to his power of description. When the loss is slight, however, it is essential to measure by some such instrument as that employed by Head and Holmes the number of degrees through which a segment of the limb must be moved in order to evoke appreciation of movement and its direction, the figures thus obtained being compared with a corresponding set of readings from a control patient or with the average normal.

The recognition of two points applied simultaneously to the skin was tested usually over the palms of the hands, the palmar surface of the tips of the fingers, the soles of the feet, and in some cases the sur-

face of the forearm, of the leg, and of the thigh. In recording the patient's answer, ten double touches and ten single touches on each area were charted, according to the formula used by Head and Rivers, and, in order to compare the results with the normal, the maximum threshold, that is the smallest distance of the points apart necessary for a complete series of correct answers, was determined in each place.

In testing the appreciation of vibration a large tuning-fork (C.^{v} 128) was used. The fork was made to vibrate strongly, and was then placed on some definite part of the patient's limb, and if he appreciated the vibration he was told to say immediately when he ceased to feel it. The fork was then transferred to the corresponding part of the limb of a control patient, and he was told to say immediately it ceased to vibrate. This was repeated several times, and the results were tabulated.

In order to eliminate as far as possible the factor of physiological fatigue which might have accounted for the control's appreciation of the vibration after the patient had ceased to feel it, a set of readings was taken in the reverse order, the fork being placed first on the control and then on the patient. These double readings could then be compared, and, if necessary, added together. Some precaution of this sort in testing vibration is the more necessary for, as Neutra has pointed out, even in the normal individual, vibrations may be appreciated on the one limb after they have apparently ceased on the corresponding point of the opposite limb.

The recognition of form, shape, size, and weight was tested by using standard objects, such as those introduced by Head and Holmes. The ability to recognize form—that is, three dimensional objects — and shape—or two dimensional objects—is evidently not measurable, but a threshold to the recognition of size and weight can be obtained by ascertaining the relative difference that can be recognized in the size or weight of similarly shaped objects applied successively. The appreciation of roughness was tested with Graham-Brown's æsthesiometer.

Owing to the bilateral character of the symptoms, it was found necessary to introduce, especially in the cases where the loss was of moderate degree only, some method of control or some normal standard. It was found useful, therefore, to examine, side by side with each patient, a normal person, or one normal as far as sensation was concerned, of about the same age and intelligence as the patient, and to compare the different results of the examination as found in the patient with those found in the control. It was considered

important, in order to strike a normal average, not always to use the same control, and in most instances, therefore, a different control was used for each patient.

In all those forms of sensibility which were measurable, such as the appreciation of movement, the recognition of compass-points, the appreciation of vibration, and the recognition of differences of size and weight, measurements over a series of readings in the patient were compared with measurements in the control. In this way slighter degrees of loss could be rendered apparent, and the subjective element on the examiner's part eliminated as far as possible.

It must be recognized, however, that although measurement may seem to make the tests and conclusions drawn from them more exact, there is considerable danger of error and confusion if proper precautions are not adopted. Measurements have a relative value only, as they depend largely on the intelligence of the patient and the readiness with which he responds. This difficulty can be obviated, however, by the examination of a considerable number of patients and the employment of controls of the same social status, education, and intelligence as the patient. It is obviously impossible to attain accurate results in such an investigation as this if the measurable defects are compared only with such an average as may be obtained in a psychological laboratory.

The following case will illustrate the methods adopted in the examination of the patients for this paper, and will show also the character of the sensory loss that is found in a somewhat advanced stage of Friedreich's disease.

A. H., aged 23, is the eldest of a family of four children; one of his sisters, aged 16, has Friedreich's disease.

When he was 7 years old his parents first noticed that he was unsteady in his walking and seemed unable to stand properly. He was taken to hospital and was admitted for about six weeks. The unsteadiness in his gait, however, continued, and his subsequent history indeed was mainly one of gradually increasing reeling and staggering with, at times, apparently acute increase following intercurrent illness. At length, a few years ago, he became unable to walk at all, and now he can barely stand even with much support. His arms and his hands, he says, began to be unsteady in their movements soon after his legs were affected, and his speech, he thinks, gradually became jerky and difficult after an illness at about the age of 16. Except for the intercurrent periods of illness, after which his legs would always seem worse, his general health has been fairly good.

He is a thin, pale, rather undersized lad, somewhat sleepy looking, but quite intelligent. On examination he shows all the usual signs of Friedreich's

disease, the nystagmus, the explosive speech, marked scoliosis, much pes cavus, absent deep reflexes, and extensor plantar responses. All his limbs are very hypotonic and there is much inco-ordination and over-action in the movements of his arms and legs. His legs also are weak and slightly wasted. His back is weak and the muscles there, too, lack tone, so that he is very unsteady when sitting up unless he has some support to lean against.

His sensory loss is very considerable.

In the upper extremities he could appreciate all light cotton-wool touches quite well, except on the distal parts of the back of the fingers and on the palms of the hands, that is on hairless parts. Over these areas there seemed to be some hypoæsthesia. On the trunk his responses to cotton-wool touches were good. On the lower extremities he seemed to appreciate light touches quite well above the knees, but on the legs relatively heavy touches with cotton-wool were often necessary, and on his feet he missed many contacts, even when the wisp of wool was drawn to and fro. When some patches were shaved on the legs and thighs it was found that he could usually appreciate light touches even then, except on the lower parts of the legs, where he missed a considerable number. It seemed, therefore, that he had some tactile loss on his feet and the lower parts of his legs, the upper limit of which shaded gradually into the normal areas higher on the limbs.

Light pressure-touches with the finger were appreciated quite well everywhere on the upper and lower extremities and on the trunk. There was no distal loss whatever on the limbs to this form of stimulus.

To pin-prick no definite loss was noted anywhere. He seemed to appreciate the point of the pin well, even over the legs and the feet, and he admitted no difference in sharpness when areas towards the distal extremity of the limbs were compared with areas higher up. Pressure-pain readings taken with the algometer were undoubtedly high, especially on his hands, but making allowance for the variability of the results obtainable with this instrument, I could not say there was definite pathological loss.

Tubes of hot and cold water of very moderate degrees of difference of temperature were always appreciated quite correctly, even over the distal parts of the legs. His answers to these, as to the pin-prick, were ready and accurate.

In localizing any point stimulated on the surface of the body or limbs he made a few mistakes, but the errors were not definitely outside physiological limits.

In the upper extremities there was very great loss of the recognition of position in the fingers of both hands. When asked he frequently said he had no idea of the position in which a finger was, and when told to imitate the position of the fingers of one hand with those of the other, he was often quite wrong. He had very great difficulty also in finding the position of one finger with the other when his eyes were shut, very much more than his ataxia would account for. As his arms lay by his side the fingers and even the forearm tended to move about irregularly, as is common in limbs in which there is severe loss of the sense of position.

Passive movement was very poorly and very slowly recognized in the

fingers, at the wrists, and even, though in less degree, at the elbows on both sides. A large range of movement could be passed through before he recognized that any movement had taken place; he did not, for instance, recognize passive movements of his right forefinger until it was moved through a much greater angle than normal, and when he did recognize that a movement had taken place he frequently could not tell its direction. This is well shown by the following readings of the angles subtended by the minimum movements of the forefinger necessary to evoke recognition in his case and in the case of a control patient:—

	Control					
Extension	1	1	1	<1	<1	
Flexion	1	1				<1

	Patient											
Extension	25	nil.	25	nil.			27	40	?	30	nil.	
Flexion	20	30	nil.	25			30	25		25		

In these readings the "nil" placed after the number of degrees means that, though at this number of degrees he recognized that a movement had taken place, he could not describe its direction; a query means that he was in doubt.

In the lower extremities also there was very gross loss of the sense of position, and he had really very little idea of the position his foot occupied in space. He could recognize that his great toe on either foot was being touched when the examiner grasped it, but could not tell whether it had been moved or not, and could not describe what position it was in at any given moment. His loss of recognition of position and of appreciation of passive movement at the ankle as well as in the toes seemed complete. At the knees the recognition of position and of passive movement was very poor, while at the hips the loss was very much less.

The range of passive movement at his knee necessary to evoke recognition and that in the case of a control gave the following results:—

	Control								
Extension	<1		<1			<1			1
Flexion		<1		1	<1	<1		<1	1

	Patient											
Extension	35	nil.		23		35	nil.		28	35	nil.	
Flexion		21		17			21	19			15	

His power of recognizing two simultaneous contacts was grossly defective. On the ulnar border of both palms he gave wrong answers with the compass-points even 7 cm. apart, whereas the control gave a correct reading quite readily with the points at less than 1 cm. apart. The readings at 7 cm. on the right hand were:—

1	XII			I	I		XXII		I
2		XXX	I	XX				XIX	I

Over the palmar surface of the tip of the middle-finger of his left hand, where a normal individual will recognize simultaneous contacts with compass-points 2 mm. apart, he was grossly wrong when the compass-points were 2 cm. apart, the readings being

1			XI					XIIXX					I		XX						
2	II			XX							IXX		I			IX					

and over his forearm he made many errors with the compass-points 15 cm. apart. The loss was so great, therefore, that it was impossible over the hands to get a maximum threshold. Over the lower extremities also the loss was profound. With the compass-points at a distance of 12 cm. from each other on the sole the errors were so numerous that he was obviously guessing. The reading at this distance was

1			II				IXXII					X		XX							
2	X			ID						XX			I			XIXI					

His foot was so deformed that this distance extended from the heel to the ball of the great toe, so that here too it was impossible to get a threshold for correct answers. The control gave correct answers readily over the sole with the compass-points 3 cm. apart.

In the feet and up to the knees the appreciation of vibration was extremely poor. On different parts of the left foot, he could not appreciate even the strongest vibration and on the right he could recognize it very slightly. On the left leg and up to the left anterior superior spine of the ilium he failed to appreciate the vibrating fork at all, while on the right it evoked a slight sensation only. Over the ribs on both sides he could recognize it, while on the hands again and the wrists and lower parts of the forearm on both sides there was a very large amount of loss.

When his appreciation of form was being tested, his answers were slow and were frequently wrong, even though the objects had all been shown to him before the examination began. Thus he made four mistakes out of twelve trials with the right hand, and seven out of twelve with the left. When he was given ordinary objects such as a knife or a coin that he had not been shown before the examination began, he fumbled with them and usually failed to name them.

He was also unable to recognise two dimensional shapes on his palms, usually replying that "he didn't know," or "he couldn't feel the shape of it," or else answering wrongly and hesitatingly.

His appreciation of differences in size was less disturbed, but showed definite defect. He nearly always recognized correctly a difference of 1 cm. in the diameter of two discs 3 and 4 cm. across, and sometimes distinguished between discs 3·5 and 4 cm. in diameter.

His appreciation of differences in weight showed definite defect. When 100 and 200 grm., or even 50 and 200 were compared on his supported hand he was as often wrong as right, and even with 100 and 200 grm. tested on his unsupported hand half his answers were wrong. He was, however, able to distinguish readily between 500 grm. and 100.

His threshold to roughness measured with the Graham-Brown æsthesiometer was a little high on the palm and sole, but not grossly so.

The sensory loss found in this patient then, briefly, includes slight tactile loss over the distal parts of the upper and lower extremities with preservation of the cutaneous sensibility to pain, temperature, and pressure-touch; gross loss of the sense of position and of the recognition of passive movement in the distal joints especially, in all the limbs, and severe disturbance of the appreciation of vibration and of the power of recognizing simultaneous contacts on the distal parts of the upper and lower extremities; with some defect or even marked loss in the recognition of form, shape, size and weight in both hands. That is to say, the sensory loss falls very lightly on the sensibilities of touch, pain, and temperature, and very heavily on the elements of local and spatial discrimination, those elements, in a word, whose spinal path has been considered to lie in the dorsal columns.

A sensory loss similar in character to this would seem to occur frequently in Friedreich's disease. Out of the twenty patients examined for this paper, I found it present definitely in eighteen. It was not always so intense as in this patient, while in some others it was even more evident. The case I have described is obviously an advanced one, and I have purposely described it in order that the peculiar character of the sensory loss might be more easily seen. The patients examined, however, represented all stages of the disease from the early to the late, and, in like manner, the sensory loss they exhibited is of all degrees of intensity and varies from very slight to very great, but wherever it was present it always fell most heavily on those elements of sensibility chiefly affected in the case just described.

In the early stages of Friedreich's disease no definite sensory loss may be demonstrable. One of my patients was a little girl, aged 7, who was a member of a family in which Friedreich's disease occurred, but the only signs of it she presented were absent knee-jerks and slight uncertainty of movement hardly more than a choreiform restlessness of the head and shoulders. She had no obvious sensory loss. In other early cases, the sensory loss may be very slight and usually, indeed, those forms of sensibility that were least affected in the advanced cases were intact in the early ones. Amongst all the advanced cases the loss was easily demonstrated and was invariably profound and striking.

While the sensory loss, generally speaking, is in proportion to the stage of the disease, in many cases there is no correspondence between the motor disability and the amount of sensory loss. In some

cases the loss is much greater than the symptoms would lead one to expect, in other cases it is much less.

In some patients amongst those whom I examined, the affection of certain of the elements of sensation, especially of the sense of position, and the recognition of simultaneous contacts and of vibration was pronounced, and yet the ataxia was very moderate. These seem to be cases that progress very slowly, and years after the onset, when the disease is undoubtedly advanced, the disability seems paretic rather than ataxic. If we could assume that those elements of sensibility affected can be assigned to the dorsal columns, we might suppose that the dorsal column degeneration had far outstripped that of the cerebellar tracts, and that the chief brunt of the disease had fallen on them, and we know that the pathological anatomy of Friedreich's disease does afford us examples that would agree with such reasoning.

On the other hand, there are patients in whom the ataxia is much more marked, even in an early stage. These patients may be unable to get across a room without the help of the furniture, and yet the sensory loss, though quite definite, is far from being so advanced as the greater disability of the patient might have led us to expect. In these patients we must suppose an earlier and greater incidence of the disease on the cerebellar tracts. Between these two extremes all varieties are to be found, according to the relatively greater involvement of the one or the other of these systems.

It must not be assumed that the sensory loss is a more or less negligible factor in the production of symptoms. A slowly increasing loss of postural sensibility may, we know, admit of much voluntary compensation, but as the disability of the patient becomes more advanced, it is undeniable that the loss of sensibility tends to play an important part in the production of his final condition, just as it does in tabes dorsalis. I have found no patient, so advanced as to be unable to walk, in whom the sensory loss was not gross in character.

Generally speaking, the different elements of sensibility affected in any given case were affected in the same relative degree as in the case described; for example, amongst the elements of cutaneous sensibility, if these were involved, touch was usually more disturbed than cutaneous pain or thermal sensibility, while the sense of position, the recognition of simultaneous contacts and the appreciation of vibration were more affected than the appreciation of form, shape, size and weight, and if the former group was only slightly affected then the latter might be intact.

In all cases the sensory loss occurs earlier and affects the lower

extremities much more than the upper. It is almost invariably distal in type, and although not infrequently one limb may show a greater loss of the same form of sensibility than its fellow, it is more or less symmetrical on the two sides.

The peculiar character of the loss that occurs will be seen more readily, however, if we analyse the disturbance of the different elements of sensibility and see with what frequency and to what extent they are, as a rule, affected.

Touch, pain, temperature.—The elements of cutaneous sensibility that we have to consider are light touch, light pressure-touch, cutaneous pain, recognition of heat and cold, and the localization of a point stimulated. It is at once obvious on looking over the results of the examination of a number of cases that these elements of sensibility are very much more disturbed in the lower extremities than in the upper. It will be more satisfactory, therefore, to consider their affection in the upper limbs and in the lower separately. On the trunk they were only very occasionally disturbed, the loss in the lower limbs having apparently spread upwards.

In the upper extremities many patients, perhaps the majority, show no affection of any of these forms of sensibility. In examining some patients we may get the impression that there is possibly a slight blunting of acuity in the recognition of cotton-wool contacts, of pin-pricks, or even occasionally of heat and cold, towards the periphery of the limb, but no definite loss can be demonstrated; it must be borne in mind that in many cases of Friedreich's disease the extremities are cold, bluish and congested, that is, are in that condition in which cutaneous sensibility is low even in the normal individual.

In a certain number of cases, however, as in the patient whose examination I have quoted in full, the blunting of acuity towards the distal parts of the upper limbs amounted to a slight, but definite, loss. Such tactile loss was present in five of the twenty patients; and two of these patients also had slight loss to cutaneous pain, and to heat and cold. None of them showed loss to pressure-touch, or inability to localize a point touched.

The tactile loss was limited in some of the patients to the hand, in some it passed up on the forearm, in one or two it was as high as the elbow, or even higher. It was never intense and had no sharp upper limit, but shaded off gradually into the normal part above. The pain and thermal loss, where these occurred, were similar in character and distribution to the tactile disturbance; in one of the patients, however,

there seemed a slight general diminution of response to pin-prick all over the body.

It was usually in rather advanced, but not necessarily bedridden patients, that this cutaneous loss was present in the upper extremities, and it was always accompanied by much greater disorder of cutaneous sensibility in the lower limbs. Many advanced cases, however, had no definite loss in the upper limbs, a circumstance that, as will be seen, was of considerable advantage in testing other forms of sensibility, such as the recognition of simultaneous contacts which require normal tactility.

Over the lower extremities, on the other hand, a considerable number of patients had more or less severe loss of tactile sensibility. Light touch was affected in fourteen of the twenty cases. This loss was always more intense than any tactile disturbance that might be present in the upper extremities, but like the latter it was distal in its distribution over the limbs and had no sharp upper limit. In some patients it was present only over the feet, in others, it extended over the legs more or less, in others again, it was present above the knee on the thighs, and occasionally it extended to the trunk. As a rule, the more advanced the disease, the higher the upper limit of the loss extended, while the more distal areas became more deeply affected, and in some advanced cases there was almost complete tactile loss over the feet or even up to the knees.

As the appreciation of light touch diminished, pressure-touch became affected also and in not a few advanced cases, with more or less complete loss of light touch over the feet and partial loss up perhaps to the knees or higher, pressure-touch was much impaired over the feet and half way up the legs.

In the lower extremities the sensibility to pain and also that to heat and cold were, like that to touch, much more frequently affected than in the upper limbs. They were both affected with about equal frequency and were never affected without some disturbance of touch. About half the patients showed loss of varying severity. It was usually of the same distal type as the tactile loss, but less severe, and in some cases its upper limit was perhaps not so high.

The localization of a point touched was never definitely affected over the lower extremities except where there was loss of tactile sensibility.

There was never disturbance of touch, pain or temperature in the lower limbs without affection of several or all of the spatial elements of

sensibility. Over the lower extremities, indeed, the cutaneous loss tended usually to increase in severity and extent as the disturbance of the power of recognising posture and vibration increased, and it was therefore more or less in proportion to either the duration of the disease or the amount of the disability present. It was not, therefore, quite so irregular and variable in its occurrence as in the upper extremities, where frequently quite advanced cases showed no affection of tactile, painful or thermal sensibility. It must be mentioned again, however, that the feet, even more than the hands, in Friedreich's disease are often bluish and cold, to such an extent as to account for much lowering of cutaneous sensibility.

In no instance did I find in either the upper or the lower extremity any cutaneous loss definitely of a root distribution. Cases have been reported occasionally, however, in which the cutaneous loss is of very unusual situation. One case recorded by Ormerod showed a complete analgesia of mask-like appearance over the face and shoulder-strap area, with a hypoalgesia over the whole body, and some areas of complete analgesia on the legs, that somewhat suggested a root distribution. Another patient reported by Jumentié and Chenet had a cutaneous loss that seemed to indicate possibly a root or peripheral nerve origin. Such distribution of sensory disturbance, frequent enough in tabes dorsalis, seems to be rare in Friedreich's disease.

Subjective changes in sensibility were rarely complained of by the patients. One patient, however, with considerable distal loss on examination in the lower extremities, complained that the application of the two points of a compass to the sole of her foot felt as if something were being drawn along the sole, a phenomenon sometimes noticed in cases of tabes dorsalis also; another complained that the vibrating tuning-fork felt hot on the sole of her foot. Frequently in testing with compass-points over the hand or the sole in patients with considerable loss, it seemed as if the sensation persisted longer than in the normal individual.

Sense of position.—The appreciation of posture and the recognition of passive movement were affected in nearly all cases. In only three of the twenty patients examined was the loss indefinite or negligible. In the advanced stages of the disease the patient was unable to describe or imitate accurately the position of his lower limbs in space, and was usually quite unaware of the relative position of their distal segments. There was invariably less disturbance in the upper limbs; the patient frequently, however, could not indicate accurately by description or

imitation the position of his fingers or thumbs, and in some cases, indeed, the appreciation of posture was completely absent in these segments.

In earlier stages of the disease the diminution in the appreciation of posture was less pronounced, or was demonstrable only in the distal segments or in the lower limbs alone.

As the disturbances of the appreciation of position and the recognition of passive movements were always closely parallel, the exact extent of the affection could be more easily determined by the examination of the latter, and especially by the measurement of the smallest range of movement necessary at any joint to evoke appreciation or recognition of its direction. In one patient, for example, who had symptoms for six years, and in whom the disease had reached a stage in which gait was very unsteady and the movements of the upper limbs were badly co-ordinated, the smallest appreciable passive movements of the forefinger and those of the forefinger of a control examined alongside him subtended the following angles.

Control

Extension	1°	1°			<1°	<1°			
Flexion			<1°	1°			1°	1°	1°

Patient

Extension	12°×		25°	20°×	40°			30°	
Flexion		26°				26°	15°		27°

In every instance the control could describe the direction of the movement correctly; where the figures are marked with a cross or a query, the patient was either wrong in describing the direction or was uncertain.

In many cases the disturbance was so obvious that measurement was unnecessary, while in other earlier cases it was only by the comparison of readings taken from the affected and the normal that the diminution of sensibility could be definitely determined.

For instance, one of the patients has complained of slight symptoms for three years, and is now a little unsteady on her legs, but can use her hands well enough to work every day in a chocolate factory. The loss of appreciation of position in the great toes is quite definite, while readings of passive movements of her left forefinger gave the following result:—

Extension	14°	13°				8°		10°	9°
Flexion			15°	12°	10°		10°		12

At the other extreme are patients at whose wrists or knees a full range of movements may be carried out without the patient's recognizing, unless by vision, that any movement has taken place.

The distal segments are the first affected, and some disturbance can be demonstrated in the great toe, the thumb, or the fingers, even in the early stages of the disease; but as the disease advances the more proximal segments are gradually affected, though in a few cases with very pronounced defect, amounting almost to complete loss at the great toe, there was very little demonstrable loss at the knee. In these patients the symptoms progress very slowly and they remain able to walk fairly well for a long time.

The relation between the amount of loss present in the upper and in the lower extremities varied considerably in different patients, although it was always greater in the lower limbs. In some early cases the difference was slight, in others it was profound. A complete loss at the toes usually occurred in a much earlier stage of the disease than at the fingers, and a grossly wrong reading at the knee-joint could not infrequently be obtained, while it was much less common at the elbow.

The loss was generally more or less symmetrical on the two sides, but it was not uncommon to find slight differences between the corresponding joints on opposite limbs. Such differences occur all through the examination of all the forms of sensibility in Friedreich's disease, but are never at all pronounced.

In testing patients with any marked disturbance it was noticed repeatedly that the patient was able to recognize that a movement had taken place before he could distinguish its direction. This is merely an exaggeration of what occurs in the normal individual, in whom, however, the interval between the recognition of the movement and its direction is so small as to be negligible. From the consideration of some instances of early loss at certain joints, however, it seemed probable that the initial disturbance might be either an inability to decide the direction of movements that were recognized or that a movement and its direction were simultaneously recognized, but only when of a larger range than was required in the normal; that is to say, either the sense of position or the recognition of passive movement might seem to be first at fault.

The compass-test.—The examination by means of compass-points is an easy test to carry out, because of its precision and because of the ease with which it can be recorded, features which made it an extremely satisfactory test in the examination of some of the early cases.

It was usually tested only on the distal segments of the limbs, but in some cases higher up over the forearms, legs, and even thighs. The necessity of establishing normal thresholds for so many different parts of the body restricted the use of the test on the proximal segments of the limbs and on the trunk, and the examination of the distal parts of the limbs was quite sufficient in most of the cases to demonstrate loss to this form of sensibility.

In all but the very earliest cases some disturbance was found. This occurred roughly with about the same frequency as did loss of the sense of position, and, like the latter, it varied very much in different patients, but seemed to show a gradual progression from slight defect in the early stages of the disease to gross loss in the more advanced stages. For instance, while most normal individuals can distinguish two points readily at 1 cm. apart on the palm, an early case of Friedreich's disease may give a poor reading at this distance, and may require the points to be 2 or 3 cm. apart before a series of correct answers is possible; while an advanced case may show such great loss that the two points cannot be distinguished as such when they stretch the whole length of the palm.

One patient in a comparatively early stage of the disease gave the following readings on the left palm with the points at 4 cm. apart:—

| | | |

While the appreciation of simultaneous contacts and the knowledge of position were affected with more or less the same frequency, they were affected also with about the same relative intensity in the different stages of the disease. It was found repeatedly that a moderate or a gross loss of the one form of sensation was present side by side with a parallel loss of the other. Occasionally, however, the loss of position might be slight, while the failure to recognize simultaneous contacts was quite marked. Less frequently again, it happened that the loss of position seemed relatively a little greater than the loss in appreciation of double contacts.

Like the loss of the sense of position, the defect in appreciating double contacts is always greater in the lower extremities than in the upper, and like it too it is usually more or less symmetrical on the two sides of the body. The tactile loss present in the lower extremities frequently interfered very considerably in the examination with compasses. In such patients the disease is usually so advanced that much error is found over the upper extremities and in the proximal portions of the lower limbs where the tactile loss is either absent or very slight.

I have observed, however, cases in which there was no demonstrable disturbance of tactile sensibility or, at the most, only a slight hypoæsthesia on the distal segments of the lower extremities, in which, nevertheless, the appreciation of two contacts was profoundly affected and grossly out of proportion to the tactile disturbance. Not only, therefore, could loss to compass-points be demonstrated in almost every case in regions in which there was no tactile disturbance, but where slight tactile loss existed the failure to appreciate double contacts was out of all proportion greater and evidently independent of it. These observations agree with the important conclusion which has been already established by the examination of clinical cases in which there is a dissociation of certain elements of sensibility, that the accuracy of the recognition of two points (that is, Weber's test) is not a measure of tactile sensibility and may be lost apart from it.

Vibration.—The appreciation of vibration was frequently and often very considerably affected. In one patient already mentioned, in whom all qualities of sensation were intact, there was of course no loss to vibration. In three others the loss was doubtful; though in each there was an apparent diminution according to actual measurement and comparison with the controls employed, the difference between the patient and the control over a series of readings was within the limits of physiological difference between two normal individuals of the same

intelligence as the patients. In all the patients except these, the loss to vibration was beyond doubt, and in many cases was very pronounced.

Not only patients in the advanced stages of the disease, but many even of those able to get about quite well, may show a very marked diminution in the appreciation of vibration. In more than half of the patients the loss over some part of the body was so great that measurements were unnecessary; on certain areas the vibration was not appreciated at all.

The following example will serve to illustrate the degree of loss that may be present in a moderately early stage of the disease. One patient has had symptoms of Friedreich's disease for about four years and is now a little ataxic, but can walk fairly well. She could not appreciate the strongest vibrations of a fork on her left foot and leg, while on the right leg she could do so for about one-third as long only as the control.

Like the loss of other forms of sensibility, the diminution in the appreciation of vibration is often asymmetrical. The difference between the two sides may be recognized by the patient, who may say, "Oh, I feel it more on that side," or "it's quite different there."

In the earlier stages of the disease the loss of appreciation of vibration was always greater on the lower extremities than on the upper. As the disease advances the loss increases in the upper extremities, and may finally, in very advanced cases, be almost complete in both upper and lower limbs.

The systematic examination of a number of cases, however, shows that the diminished appreciation of vibration is not confined to the limbs, and though it is generally greater in the distal than in the proximal segments of the limb cannot be described as a distal loss in the sense in which this term was used, for example, with regard to tactile hypoæsthesia. As the disease advances, the disturbance tends to spread from the legs over the trunk, and, while in an early case there may be only some diminution in the feet, in an advanced case the loss may reach as high as the clavicles. Usually it diminishes gradually in severity from the feet upwards, and may be more pronounced over the ilium than over the hand. It would seem, therefore, that if the impulses underlying the appreciation of vibration are conveyed by the fibres of the dorsal columns, sensibility thereto is lost first in the areas that send impulses upward through the longest fibres of these columns, and the affection gradually and successively involves the fibres according to their length.

The disturbance in the appreciation of vibration frequently, therefore, seems more diffuse and widespread over the body than the defect in the recognition of posture or in the appreciation of double contacts. Occasionally, however, the appreciation of vibration was less affected than these other two; and, in general, it must be admitted that though in different patients one or other of these forms of sensation may appear the more affected, as far as we can compare such very different qualities the relative intensity of the loss of each is roughly parallel. All three show the same bilateral variations and the same tendency to the earlier and greater incidence of the loss on the lower limbs.

Form.—The recognition of form, or three-dimensional shape, was much less affected than the sense of position and the appreciation of simultaneous contacts and of vibration. It must be remembered, however, that this test could be applied in the upper extremities only where the general intensity of sensory loss was slight and much less than in the lower limbs. Further, the recognition of form is a very complex quality and depends on the cortical elaboration of impulses which pass along several paths. Moreover, the test as used in these observations is a qualitative one and could not be varied.

It was examined in seventeen of the twenty patients only. Of these ten replied readily, and named the test objects correctly; two answered slowly, fumbled the objects considerably in their hands, but named them correctly in the end; three answered slowly and made occasional mistakes, while two made frequent mistakes, and seemed to show quite definite or even gross loss in recognizing the form of the different objects.

Notwithstanding its much less frequent occurrence, the defect in the appreciation of form would seem to be more associated with the disturbance of the sense of position, the recognition of double contacts, and the appreciation of vibration than with tectile loss. In the two patients that answered very badly, tactile sensibility in the upper extremity was very slightly affected in one, and not at all in the other; and in the five that answered slowly and uncertainly, touch was never more than slightly affected in the upper extremities. The sense of position, recognition of double contacts, and appreciation of vibration, on the other hand, were very grossly affected in the two definitely marked cases, and were more or less seriously affected in the five cases of slighter loss. It would seem, therefore, that the recognition of form may be lost independently of tactile sensibility, but that its loss does not occur without disturbance of the appreciation of position, double contacts, and vibration.

It is impossible, however, to regard it as definitely proved that the loss of recognition of form is co-extensive with loss of these other forms of sensibility, for several patients showed that a very high degree of loss to these latter was compatible with slight loss only in the recognition of form. All we can infer, therefore, is that the appreciation of form is closely associated with the integrity of those paths in the cord that carry the impulses which subserve the sense of position, recognition of two points, and appreciation of vibration.

Shape.—Like the recognition of form, that of shape in two dimensions could be tested on the upper extremities only, but the frequency of its affection seemed much greater than that of form. It is, however, a much more difficult test even for the normal individual with his eyes shut to tell the shape of an object when it is pressed on his palm than it is to recognize its form when he is allowed to handle it, and the controls were not invariably correct in the tests for shape as they were in those for form. A considerable number of mistakes therefore must be regarded as within the limits of experimental error. Making every allowance, however, for the difficulty of the test there appeared altogether too many instances of gross lack of appreciation of shape to neglect this quality of sensibility entirely in estimating the sensory disturbance in Friedreich's disease.

In five patients, at least, there was gross loss; these patients were either unable to recognize the shape of the objects pressed on their hands, or made so many mistakes in attempting to do so that they seemed to have no idea of the shape at all. Most of them when allowed to handle the objects could tell the shape fairly well, except the two patients who had marked loss in the recognition of form, and who were included amongst the five patients with gross defect in the recognition of shape. There was no patient, indeed, with any loss in the recognition of form who did not also show some disturbance in the appreciation of shape, and this latter was usually much the greater.

In some of the patients with pronounced loss of appreciation of shape there was a very slight tactile loss on the hands, but in none of them did it seem sufficient to account for the inability to recognize shape. In others there was no tactile disturbance, and in none of the five patients was there any pressure-touch loss. The loss of appreciation of shape in these patients, therefore, must be regarded as occurring independently of any disturbance of tactile sensibility.

In all of the five patients the disease was considerably advanced and the loss of the sense of position, of the ability to recognize simultaneous

contacts and to appreciate vibration was pronounced or even gross in character in them all.

Size.—In testing the patient's ability to recognize size, round discs varying in diameter from 0·5 to 4 cm. were used, and were pressed firmly and evenly on his palm, the difference in diameter between any two successive discs being 0·5 cm. Usually it was found that the controls could distinguish quite easily any two discs with this difference. Greater differences were always recognized correctly.

In the majority of the patients no definite loss in the recognition of size was demonstrable. Seven patients, however, made many errors in attempting to distinguish discs of 0·5 cm. and 1 cm. difference, and even in some instances discs with a difference of 2 cm.

These were chiefly the patients who were unable to recognize shape correctly, and in some of them there was also very slight loss to cotton-wool touches over the hands. This seemed, however, hardly enough to interfere to any extent with the test, for pressure-touch was quite preserved, and other patients who had just as much tactile loss as these seemed to show no loss in the recognition of size. In all these seven patients the disturbance of the sense of position, the recognition of compass-points and the appreciation of vibration was marked, or gross.

It would seem, therefore, that a certain loss in the recognition of differences in size may be found over the palm of the hands in advanced stages of Friedreich's disease and that it occurs only in patients in whom sense of position, discrimination of compass-points and recognition of vibration are much affected, though not always in proportion to the loss of these elements of sensibility.

Weight.—The recognition of weight, like that of size, is a measurable form of sensibility, and the controls used gave very uniform results. As many as ten of the patients with Friedreich's disease were considered to show definite loss in the appreciation of differences of weight; in four of these, there was slight loss only, but six had considerable or even marked loss.

These six were the same patients that showed gross loss in the appreciation of shape, and defective recognition of size, and they included amongst them the two patients who had considerable loss in the recognition of form. They were all, therefore, in more or less advanced stages of the disease and showed in the upper extremities much loss in the recognition of position, dual contacts and vibration. In comparison with the intensity of this loss indeed, the defect in the recognition of differences of weight could not be described as very great. It seemed,

however, to be associated definitely with a gross defect in the recognition of all these other forms of sensibility, for in a few cases in which these were markedly affected, but in which one or other of them seemed spared more than the others, weight loss to any extent was not found. It could not, however, be definitely associated with any one of these elements in particular.

A disturbance of the recognition of differences of weight, therefore, would seem to be found in those patients with Friedreich's disease who have a gross loss of the appreciation of position, simultaneous contacts and vibration, and would seem, moreover, closely associated with a defect in the recognition of size and of shape, and like these two forms of sensibility would seem to occur more frequently than a loss in the recognition of form.

In examining the appreciation of form, shape, size and weight in the hands, it was noticed occasionally that there were slight differences between the two sides similar to that described for the other forms of sensibility.

We are now in a position to review the results of this analysis of the sensory disturbances found in the twenty typical cases of Friedreich's disease, in all stages that we have examined.

The appreciation of touch, pain and temperature are very irregularly affected in the upper extremities, never more than very slightly and often not at all. When loss occurs it is almost always a slight distal blunting to touch, and very rarely to pin-prick, or to heat and cold as well. In the lower extremities these cutaneous elements are more frequently involved, and there is often some distal hypoæsthesia to light touch, or even to pressure-touch, and in many cases also to pin-prick and to heat and cold. It is the other elements of sensation however, chiefly those that are commonly included in the term "deep sensibility," but also the appreciation of simultaneous contacts, and of size, shape and form, that are most severely affected. The sense of position and the recognition of passive movement, the appreciation of double contacts and of vibration are almost always more or less affected, especially in the distal parts of the lower limbs, and not infrequently, though to a less degree, in the upper limbs as well. The frequency and the constancy with which these three elements of sensation are disturbed are indeed characteristic of the disease.

The recognition of shape and form, and the appreciation of size and weight are also affected, but much less frequently and less seriously than

the sense of position, the appreciation of compass-points, or of vibration. This is probably due to the fact that these forms of sensibility can be examined in the upper extremities only where the sensory loss as a whole in the early stages of the disease is usually not great, and possibly also to the fact that they are more elaborate forms of sensibility. They would seem, however, to be associated in their disturbance rather with the loss of the sense of position, the appreciation of double contacts and of vibration than with tactile loss. The recognition of shape, and that of size and of weight are affected with the same frequency, and usually in the same patients, while the recognition of form is less often disturbed.

The elements of sensibility, therefore, which it is assumed are conducted through the dorsal columns of the cord, would seem to be disturbed in Friedreich's disease more or less constantly and characteristically. The loss, especially in the early stages of the disease, falls most heavily on the lower extremities, that is on the regions innervated by the spinal segments that are earliest affected, and tends to spread higher and higher over the body and to become more profound as the disease advances.

Those elements of sensibility that are conducted through the dorsal columns have been divided into two groups. The recognition of two points of the compasses, and the appreciation of size, shape and form which are dependent at the periphery on the integrity of the cutaneous nerve-endings would seem to run in one group; and the sense of position and of movement, the recognition of vibration and the appreciation of weight, which are dependent peripherally on nerve-endings in joints, tendons, and muscles, apparently compose another group. As the disturbance of the sense of position, of double contacts and of vibration was always so great in every case in which the recognition of size, shape, form, and weight was affected, it is impossible to correlate the disturbance in recognition of size, shape and form with that in the recognition of compass-points particularly; or the loss in appreciation of weight with that of position. In the description of the fate of these elements of peripheral sensibility, therefore, I have preferred for convenience to follow the order in which they were tested clinically, and to consider together the disturbance of the sense of position and of movement, the loss of appreciation of double contacts and the diminished recognition of vibration which constitute a more primary group; the recognition of form, shape, size and weight, would seem to compose a group of more secondary and elaborate sensations.

In a disease such as Friedreich's ataxy where there is a very slow

progressive degeneration of the dorsal columns of the cord it is inevitable that though the sensory loss may conform to a definite type there must be much variability in the relative intensity of the affection of the different elements of sensibility in different cases. The frequency, however, with which a characteristic sensory loss does occur would seem to justify its inclusion in the clinical picture of the disease as an integral, not as an exceptional, feature; and further, the constancy and regularity with which this loss involves the sensory impulses assigned to the dorsal columns of the cord goes to confirm the conclusions regarding sensory conduction in the cord that have been obtained by the clinical and anatomical study of local spinal lesions.

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THE WASSERMANN REACTION AND ITS APPLICATION TO NEUROLOGY.

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THE intention of this paper is to review the present state of knowledge of the Wassermann reaction in all particulars which bear directly or indirectly upon neurology, but in these particulars only. It is also the intention to describe fully the methods which we have ourselves utilized as being the most satisfactory according to our deductions. These deductions are based upon researches into the subject of syphilis generally, and also upon the results of a long collaboration with Dr. Henry Head and Dr. Fearnsides upon syphilis of the nervous system in particular.

The work is treated largely from the technical point of view, and thus assumes a general knowledge of the principles, and even of the technique, of the reaction on the part of the reader. We have not discussed the theory of the subject, since that has no application to neurology, neither have we reviewed the modified tests.

The paper is intended to be read in conjunction with works published or forthcoming by Dr. Head and Dr. Fearnsides and ourselves, and references to cases are constantly made by means of index numbers, which remain the same throughout all these papers.

We desire to record our indebtedness to Professor Bulloch, whose influence, we hope, may be detected throughout.

CHAPTER I.—THE TECHNIQUE OF THE WASSERMANN REACTION.

INTRODUCTION.

Since the inception of the idea of the Wassermann reaction numerous modifications have been suggested with a view to simplification and improvement. The simplified methods have usually led to the introduction of relatively fundamental alterations, and have only enjoyed a vogue when the original method has been inconvenient or looked upon as tedious. On the other hand, notable improvements in detail upon the original description have been suggested, and adopted more or less universally after laborious justification. A reduction in

the absolute quantity of the reagents is now general. Watery antigens have been replaced almost entirely by alcoholic or other extracts, and the original severity of the controls for the antigen and other reagents has long been lightened. These improvements do not, of course, enjoy universal recognition, and therefore it is found that the technique adopted by one observer commonly differs from that of another, and in this manner a certain diversity of result is inevitable. It has been suggested that a Commission should inquire into and adjudicate upon the most suitable technique to adopt, but unfortunately there is no finality in medicine, and the selected method would soon be surpassed, if, indeed, it was ever accepted.

As the result of the variety in the technique, the mere statement that a particular "Wassermann reaction" is negative is insufficient; before the value of such an observation can be appreciated, it is essential to know the methods by which it has been arrived at, and the general results which these methods usually yield. We, therefore, describe our technique in full.

Reagents.

The reagents required in the performance of the Wassermann reaction are as follows:—

(1) Antigen.
(2) Serum or cerebrospinal fluid to be tested.
(3) Complement.
(4) Hæmolytic amboceptor.
(5) Blood Corpuscles.
(6) Saline solution.

Antigen.

Ever since the earliest days of the Wassermann reaction, discussion has centred round the antigen, not only from the point of view of obtaining the most efficient preparation, but also of inquiring into the ultimate nature of the reaction.

The belief that the interaction of the antigen and syphilitic serum represented a true antigen-antibody combination was early shaken by the demonstration by Marie and Levaditi [30] that an extract of a normal liver could replace an extract of a syphilitic liver in the reaction. This discovery was again followed by the independent observations of Landsteiner, Müller and Pötzl [20], Porges and Meier [46], and Levaditi and Yamanouchi [22], which showed that the Wassermann

"antigen" differed from most true antigens in being soluble in alcohol, and was presumably of the nature of a lipoid.

From this time dated the attempts to replace the complicated organ-extracts with pure solutions of lipoids. Porges and Meier were the first to use alcoholic solutions of lecithin with advantage. Levaditi and Yamanouchi found sodium taurocholate and glycocholate to be possessed of antigenic value, and to a less extent lecithin. These last observers found cholesterin to be without effect. Hans Sachs [50] then, in conjunction with Altmann, entered the experimental field with sodium oleate, and later, with Rondoni [52], introduced the artificial mixture of lecithin, sodium oleate, oleic acid, and alcohol. This mixture was tested by Facchini [13], and Eisenberg and Nitsch [12], and found to give satisfactory results.

Noguchi [36] has endeavoured to isolate the reacting substance from alcoholic extracts of animal organs by a process of fractional solution and precipitation. In this way he separated the non-specific inhibiting and haemolytic substances from the antigenic constituents. These latter, consisting mostly of lecithin, were to be found in the acetone-insoluble fraction. This work was continued with the assistance of Bronfenbrenner [37].

A notable advance was then made by Browning, Cruickshank and Mackenzie [7 and 8], who found that, though cholesterin alone had no antigenic effect, mixtures of lecithin and cholesterin gave a particularly specific reaction with syphilitic serum.

These authors have laid it down that if the addition of cholesterin is capable of increasing the quantity of complement absorbed beyond the amount absorbed by lecithin alone, this is an indication of the syphilitic nature of the serum used.

While the study of isolated constituents of the antigen was thus proceeding, attention was also directed to crude extracts of various animal tissues. The alcoholic extract of syphilitic liver was of course widely used, but, owing to the variation in the quality of different samples, fell into disfavour in many quarters. Landsteiner, Müller and Pötzl introduced alcoholic extracts of guinea-pig heart, and Michaelis [32] human heart. This last was thoroughly tested by Thomsen [55] and Boas, and is used as a routine in the Statens Seruminstitut at Copenhagen. A slight modification by Lesser [21] utilized a watery emulsion of the residue obtained by evaporating an ether-extract of human heart. This antigen has been found by Dembowski [10] to be better than a simple alcoholic extract of heart or an extract of syphilitic liver.

Acetone extracts of dried organs have been suggested by Kolle and Stiner [19].

The latest notable advance in the preparation of antigens has been the suggestion of Hans Sachs [49] to combine the alcoholic extracts of animal organs with cholesterin, thus utilizing the increased effect of this substance demonstrated by Browning, Cruickshank and Mackenzie. The addition of cholesterin to extracts of organs was found by Sachs to endow these, however unsatisfactory alone, with properties equal to those possessed by the best syphilitic extracts. The mixtures had the further advantage of being cheap and obtainable in unlimited amount.

In order to determine the antigen most suitable to our methods we undertook a series of comparative tests upon the same sera, using different antigens [28].

We selected for comparison the following representative forms:—

(1) Alcoholic extract of syphilitic liver (Wassermann).

(2) Alcoholic extract of human heart (Michaelis).

(3) Alcoholic solution of lecithin and cholesterin (Browning, Cruickshank and Mackenzie).

(4) Alcoholic extract of animal organs with cholesterin (Sachs).

Having tested these antigens upon over 500 sera and cerebrospinal fluids we arrived at the conclusion that an antigen prepared from human heart and cholesterin showed a notable improvement upon the others, in that a much higher percentage of positive results was obtained in undoubted syphilis, while no tendency towards non-specificity was observed.

We found that in cases of manifest syphilis, primary, secondary, and tertiary combined (84 sera), the heart-cholesterin antigen gave 14 per cent. more positive results than a good syphilitic liver-antigen; 16 per cent. more than heart-antigen, and 17 per cent. more than lecithin-cholesterin antigen.

In the case of latent syphilis, that is, in syphilitic patients without symptoms and those under treatment, the improvement was still more obvious.

The advantage of this antigen was further particularly apparent in syphilis of the central nervous system including "parasyphilis." Fifteen in fifty-six of these sera gave positive results with heart-cholesterin when heart extract alone was negative. Similarly six sera in thirty-one were positive with heart-cholesterin when syphilitic liver gave a negative reaction. The poorest results were obtained with lecithin-cholesterin. When testing cerebrospinal fluid, however, the lecithin-cholesterin

antigen gave slightly better results than syphilitic liver or heart, but not so good as heart-cholesterin, six being negative out of twenty-one, when heart-cholesterin was positive.

It must be clearly understood that these figures only denote the results obtained on the actual samples tested, and have no bearing upon the relative results which might be obtained with the different antigens in other collections of cases. It may be stated that the most obvious differences were encountered in cases of "cerebral syphilis," and so much was this the case that we were compelled to discard a number of tests which had been carried out with heart-antigen for this present investigation and to start *de novo*. Whenever the Wassermann reaction is referred to in this series of papers, the use of heart-cholesterin antigen is implied.

Another highly important advantage of the heart-cholesterin antigen lies in its invariability as demonstrated by us [28]. It has been held very generally, especially in Germany, that a complete quantitative titration of a serum in the reaction is of little value owing to the great error introduced, especially by the variation in antigens. We have, however, always applied this procedure, and particularly after the works of Thomsen and Boas demonstrated its exactitude when using heart-antigen. In practice, however, it was evident that some samples of heart-antigen varied, but this variation appeared to be almost entirely eliminated by the addition of cholesterin. Thus we have always found that a quantitative estimation may be carried out with entirely different reagents and antigens at different times with a very small margin of error (*vide* p. 209).

Example showing a quantitative Test of one Syphilitic Serum, using twenty-four different heart-cholesterin antigens. Result of twelve Antigens only shown, the others were similar.

Syphilitic serum	Antigen No.											
	13	14	15	16	17	18	19	20	21	22	23	24
c.c.												
0·075	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++
0·052	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++
0·042	+++1	+++1	+++1	+++	+++	+++1	+++1	+++1	+++	+++	+++	+++
0·031	++	+++	+++	++	+++	+++	+++	+++	++	+++	++	++
0·023	+	++	++	+	+	+	+	+	+	+	+	+
0·017	0	+	+	0	0	0	0	0	0	0	0	0

(The + signs are proportional to the degree of *inhibition* of hæmolysis. Thus ++++ = No hæmolysis in the sense of a complete positive Wassermann reaction. +++1 = trace of hæmolysis.)

Since various samples of heart-cholesterin antigen of equal value can readily be prepared, it follows that this factor at least presents no difficulty in a quantitative estimation.

The heart-cholesterin antigen is prepared in the following way :—

Obtain a fresh human heart and remove from it the muscular portions of the left ventricle free from fat. It is immaterial whether the heart is diseased or not. The muscle is then passed through a mincing machine and 10 grm. of the mince are ground up with 90 c.c. of absolute alcohol for a short time with clean sand. The whole is then transferred to a stoppered bottle and shaken for one and a half hours in a "shaker" at room temperature. Finally, filter through paper and preserve in the ice-chest. The heart extract should be kept for several days before it is first used and filtered again if a precipitate forms in the cold. In a well-stoppered bottle this antigen should keep in the ice-chest for six months. A 1 per cent. solution of cholesterin (Kahlbaum) in absolute alcohol is also made up. It will be necessary to apply heat and thorough shaking to obtain complete solution. For use in the reaction three parts of the heart-extract are mixed with two parts of the cholesterin solution.

As shown long ago by Sachs and Rondoni [53], the method of dilution of antigens is important in order to obtain the best results in each case. Generally they should be mixed with the saline *slowly*. The improved effect is not present with every serum tested but in some cases it is very marked. With our heart-cholesterin antigen, however, the method of mixing does not appear to have much effect upon the antigenic properties, though it is usually found that *rapid* mixing is most efficacious. Thus this antigen should always be placed in a large test-tube and the requisite quantity of saline added *suddenly*.

A heart-cholesterin antigen approximating to our formula has been used by Walker and Swift [58]. These authors have confirmed our statements as to its properties in every particular, and they arrived at the same conclusions by independent lines of investigation. In addition they have elicited the fact that guinea-pig's heart is of equal value to human heart in the preparation of the mixture, and thus have introduced a modification which under certain circumstances may be convenient. The results of Walker and Swift confirm our belief that an antigen such as we have described is an essential for the successful carrying out of the reaction.

Serum and Cerebrospinal Fluid.

The blood to furnish the test serum was always withdrawn from the patient's thumb according to the well-known technique elaborated by A. E. Wright.[1]

This method of bleeding is much quicker than venepuncture when a sufficient skill has been acquired by practice. Suitable apparatus is essential, and so far as we are aware cannot be purchased upon the market.

The capsules are made in the usual manner from best glass tubing, about 7 mm. external diameter. The barrel of the capsule should measure 3 in. (7·5 cm.) and will thus have a capacity of about

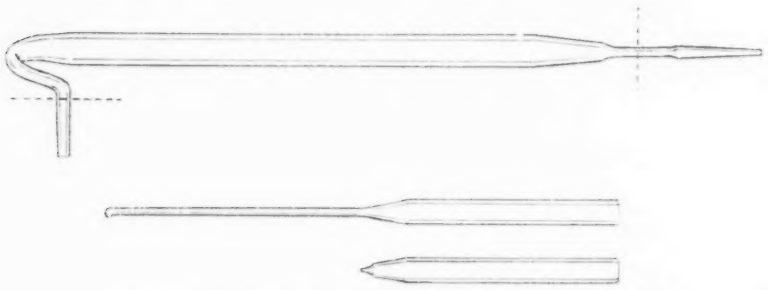

FIG. 1.—Showing the construction of a capsule and "pricker."

1·5 c.c. The curved entering end should have as wide a bore as possible. A right-angled bend is then constructed on the entering end and the glass cut off, as shown in the diagram (fig. 1). The straight end of the capsule is drawn out to a short point to facilitate sealing after use.

The "prickers" are made from narrower glass tubing about 5 mm. external diameter. The glass is first drawn out to make two pipettes and then the capillary part of the tube near the shoulder is again drawn out in the Bunsen bye-pass. The point thus made is broken off short as in the diagram (fig. 1).

Proceed as follows: The right hand of the patient is smartly shal downwards, either by the patient himself or by the operator, in orde drive the blood into the finger-tips. If the hand is previously col should be warmed in hot water. Then without delay a piece of rul

[1] For general principles and methods see Sir A. E. Wright, "Technique of the teat capillary glass tube." London, 1912. Constable.

tubing [5 mm. diameter and 18 in. (about 45 cm.) long] is wound round the right thumb from the base to the joint. The first turn of the tubing is locked by the second (*see* fig. 2), and the last is secured by the operator's left index-finger placed on the pulp of the patient's thumb, the operator's thumb being placed against the patient's knuckle, thus compressing the distal phalanx of the thumb.

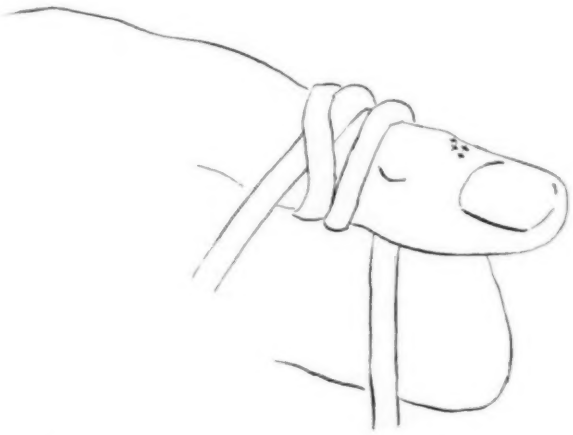

FIG. 2.—Showing the tourniquet in position and the site of the punctures.

Four rapid stabs are then made at the point indicated by crosses, this point being held uppermost. The blood which issues may be collected at the site of the punctures or may be allowed to collect in a pool at the base of the patient's nail. The curved end of the capsule is then applied to the blood in such a way that the body is at the lowest point (fig. 3). The blood will then run in by gravity, being assisted by a "scooping" motion of the capsule. When no more can be expressed the remnant of blood is wiped away, the tourniquet removed and the whole process repeated until the capsule is two-thirds full. It is, however, unnecessary to puncture the thumb a second time. During the operation the capsule may be placed on the table with the short bend at the entering end pointing upwards.

In the case of a "full-blooded" individual the requisite quantity of blood may be collected at one application of the tourniquet, but others may require four or five. When the capsule is two-thirds full the

straight end is sealed in a flame and, after clotting has taken place, the blood is shaken down into the closed end.

The clot is separated from the serum in the centrifuge, but before centrifuging the curved end is cut off, as otherwise the capsule is apt to break. The tube is also numbered with grease pencil. After centrifuging for a minute or two, the tubes are supported on end in "plasticine" and the serum is pipetted off and inactivated at 55° C. for thirty minutes in the water-bath. The pipettes may be carried in a

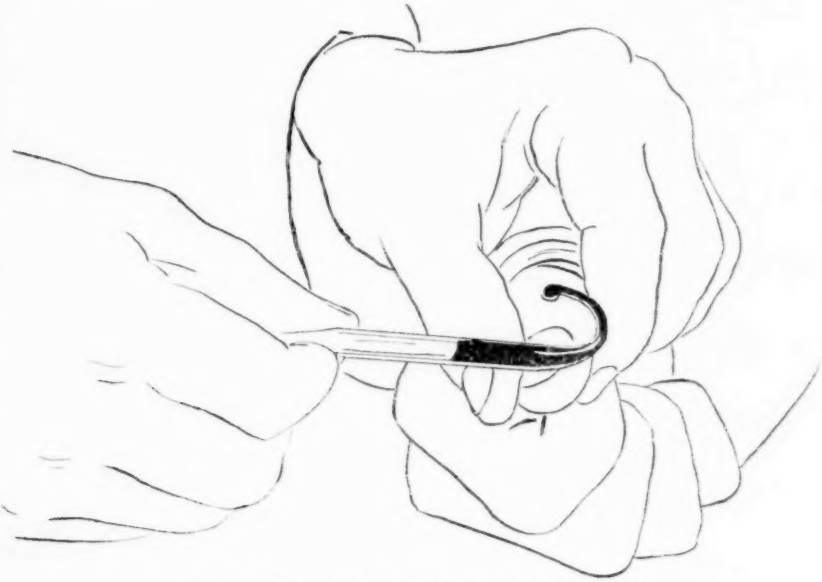

FIG. 3.—Showing the general position for bleeding.

float as shown in the figure (fig 4). It is desirable to inactivate the serum within twenty-four hours after bleeding, and in this condition it will retain its properties for a long time.

The effect of heat upon the test fluids.—In the case of serum there is no difference of opinion as to inactivation. It is always heated. With the cerebrospinal fluid, however, the practice of different observers varies.

We have always used this fluid *unheated*.

So far as concerns the neurological literature dealing with the Wassermann reaction, we have been unable to find much reference to

the effect of heat upon the reacting substance. It will be remembered that originally upon the introduction of the reaction, it was stated that the test-serum must be "inactivated" in order to destroy any

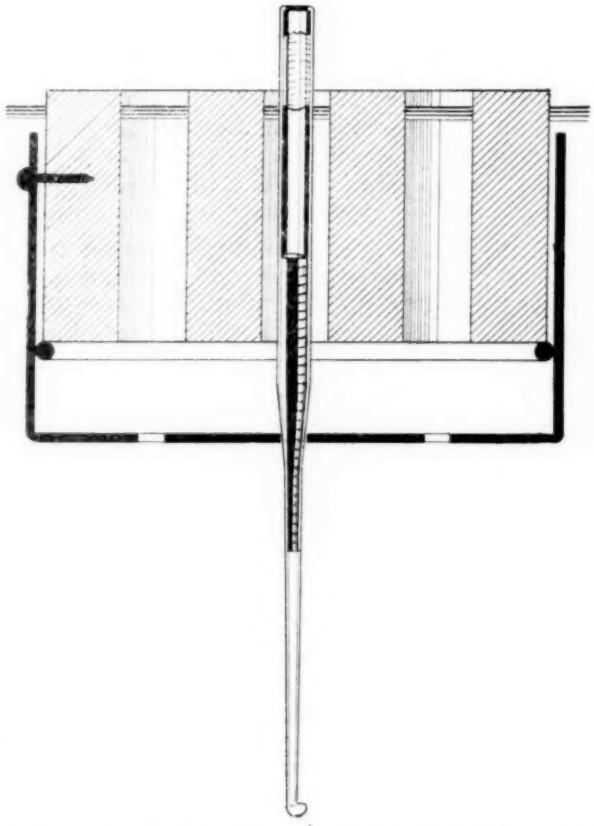

FIG. 4.—Section of the "float" used for supporting the pipettes in the water-bath.
A circular copper box is fitted with a large cork stopper (oblique shading). This stopper is held in position by a pin at the side, and rests upon a shelf of copper wire. It is pierced with eight circumferential holes and one central; these correspond in position with nine smaller holes in the bottom of the copper box. The size of both sets of holes is so adjusted that a pipette will readily pass through the cork and rest with its shoulder upon the copper. The contrivance, when fully loaded, will float with its upper surface on the water level.

normal complement, which would interfere with the Bordet-Gengou phenomenon. It was, however, soon shown by Sachs and Altmann [51] that such inactivation was most necessary because a non-syphilitic

"active" serum might give a positive Wassermann reaction. Numerous instances of such were given by Boas [4] and by ourselves. If inactivation was omitted a syphilitic serum might give a negative result by reason of excess of complement, while a non-syphilitic serum might give a positive owing to the presence of a non-specific thermolabile body [24].

The nature of the body in a normal active serum which gives a positive Wassermann reaction has not been studied in much detail, and is usually looked upon as similar to the true Wassermann substance. Noguchi [35] was among the first to study the effect of heat upon the serum and demonstrated that a temperature of 55° C. produced a very marked destruction of the "syphilis antibody," to such an extent that at the end of thirty minutes 25 per cent. only of the previous content was available. The most rapid destruction took place in the first five minutes. Noguchi appeared to look upon the bodies destroyed as true Wassermann substances, although he admitted that a normal active serum contained non-specific bodies which were capable of giving "Wassermann reactions" with certain fractions of an alcoholic antigen. He therefore introduced his special antigen which was designed for use with active serum, in order to avoid loss by heat; this antigen did not react with the non-specific body in the serum.

Thomsen and Boas [56] also looked upon the reacting substance as destructible by heat in variable degrees. They considered that substances might appear in the serum in the course of several diseases, including syphilis, which gave a positive Wassermann reaction. These diseases, however, generally differed from syphilis in that the reacting substance was more easily destroyed by heat in the former than in the latter, and thus in them the reaction would be negative. But, in syphilis also, the reacting substance in primary and latent syphilis was more readily destroyed than in secondary cases; thus these would tend to be negative while the secondary sera were positive.

We have found the effect of heat upon the serum to be as described by Noguchi and have also noted that an "active" serum from a patient with latent syphilis (giving a negative reaction on inactivation), contains more non-specific reacting substance than a normal active serum. Nevertheless, we are not altogether disposed to look upon the non-specific reacting body as similar to the Wassermann body, nor to admit that the Wassermann body is in fact destroyed by heat to such a marked extent as is usually stated.

In order to test the matter more accurately we have utilized the

Wassermann body as found in the cerebrospinal fluid, since in this way the difficulties associated with the complex constituents of serum may be avoided. The cerebrospinal fluid contains none of the non-specific reacting body which is present in an unheated serum.

We have found that in dementia paralytica and tabes dorsalis heat does not materially reduce the strength of the reaction as found in the cerebrospinal fluid.

Experiment showing the Effect of Heat (55° C.) upon the Reaction of the Cerebrospinal Fluid in two Cases of Tabes dorsalis.

Example 1.

Amount of cerebrospinal fluid	Unheated	Heated in water-bath for Minutes						
		5	10	20	30	40	50	60
0·2 c.c.	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
0·1 ,, ...	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
0·05 ,, ...	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
0·02 ,, ...	+ + +	+ + +	+ +	+ + +	+ +	+ +	0	0
0·01 ,, ...	0	0	0	0	0	0	0	0

(+ + + + = Positive reaction. 0 = Negative.)

Example 2.

Amount of cerebrospinal fluid	Unheated	Heated in water-bath for Minutes				
		5	10	20	30	40
0·2 c.c.	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
0·1 ,, ...	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
0·05 ,, ...	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
0·02 ,, ...	+ +	0	0	0	0	0
0·01 ,, ...	0	0	0	0	0	0

(+ + + + = Positive reaction. 0 = Negative.)

In cerebrospinal syphilis, however, the effect of heat is somewhat more marked, although even in this case it falls far short of the apparent effect observed in the case of serum.

Experiment showing the Effect of Heat (55° C.) upon the Reaction in the Cerebrospinal Fluid in two Cases of Cerebrospinal Syphilis.

Example 1.

Amount of cerebrospinal fluid	Unheated	Heated in water-bath for Minutes			
		5	10	20	30
0·2 c.c.	+ + + +	+ + + +	+ + + +	+ + + +	+ + +
0·1 ,, ...	+ + + +	+	0	0	0
0·05 ,, ...	0	0	0	0	0
0·02 ,, ...	0	0	0	0	0
0·01 ,, ...	0	0	0	0	0

(+ + + + = Positive reaction. 0 = Negative.)

Example 2.

Amount of cerebrospinal fluid	Unheated	Heated in water-bath for Minutes			
		5	10	20	30
0·05 c.c.	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
0·02	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
0·012	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
0·006	+ + + +	+ +	+ +	+	+
0·003	0	0	0	0	0

(+ + + + = Positive reaction. 0 = Negative.)

We, therefore, conclude that inactivation of the cerebrospinal fluid does not lead to any material destruction of the reacting substances except in cerebrospinal syphilis, and even in this case the destruction is slight when compared with that which occurs in the serum. In our view this result is explicable on the assumption that the Wassermann body proper is practically unaffected by heat. In those cases, however, in which the syphilitic process is most active (cerebrospinal syphilis) the cerebrospinal fluid contains additional bodies derived from the blood fluids in the form of an acute exudate, and these bodies not only tend to give a stronger Wassermann reaction, as in the case of "active" serum, but are also more thermolabile.

It will be remembered from the work of Weil and Kafka [59] that in acute infective meningitis the cerebrospinal fluid contains the normal "anti-sheep hæmolysins" of the serum, both amboceptor and complement. In dementia paralytica, on the other hand, no complement was present and the amboceptor in less amount only. These authors suggested this phenomenon as a means of differential diagnosis between dementia paralytica and acute meningitis. They did not, however, test the cerebrospinal fluid from the acuter cases of syphilitic meningitis. In our view their work suggests that in the acuter cases, whether syphilitic or not, the constituents of the cerebrospinal fluid tend to approximate more nearly to those of the serum than in the chronic cases (dementia paralytica and tabes dorsalis, &c.). The non-specific body of the serum will therefore be found in the cerebrospinal fluid in the acute syphilitic lesions more often than in the chronic. Thus the use of unheated cerebrospinal fluid in the cerebrospinal cases in particular will determine a stronger reaction than heated fluid, and, no doubt, this stronger reaction will be to some extent "non-specific" as in the case of unheated serum, but in practice this "non-specificity" is negligible. An unheated cerebrospinal fluid does not give a positive

Wassermann reaction except in a case of syphilis of the central nervous system, and, therefore, inactivation of this fluid should not be carried out.

We have no doubt that neglect of this precaution has occasioned some of the poor results recorded by those who follow the "original" technique.

It is not possible, however, to determine exactly to what extent this disturbing factor is present owing to the absence of technical data in many published papers, and to the use of loose expressions as to the "original method" in use. The "original method," as now described by the great authority Plaut [43], requires the use of an aqueous extract of syphilitic liver and inactivation of the cerebrospinal fluid. G. Meier [31], on the other hand, who has also been closely associated with Wassermann, now uses an alcoholic extract of syphilitic liver, while cerebrospinal fluid—"braucht nicht inaktiviert zu werden." Clearly, therefore, the use of the expression "original method" conveys a different meaning in the writings of different observers.

The use of unheated cerebrospinal fluid increases the reacting power of this substance in many cases, but at the same time it puts an end to any exact comparison between the strength of the reaction in the heated serum and the unheated cerebrospinal fluid. This factor must not be lost sight of throughout this paper, as, also, the fact that twice as much cerebrospinal fluid as serum is always used.

The quantity of test fluids.—In addition to the question of heat, much variety in practice is found relating to the *quantity* of cerebrospinal fluid used in the test. Most observers use the same amount of serum in proportion to the other constituents. In the original reaction 0·2 c.c. of cerebrospinal fluid was used in a total volume of 3 c.c. in the fixation stage. It was soon found, however, that more fluid could be used without endangering the result; thus Boas and Lind [6] used 0·4 c.c. in a volume of 3 c.c., and we have always used a maximum of 0·2 c.c. in a volume of 1 c.c. Latterly much attention has been directed in neurological circles to the quantitative method ("Auswertungsmethode") of Hauptmann and Hössli [17], the chief object of which is to use still larger quantities. These observers use a maximum of 1·0 c.c. of cerebrospinal fluid in 3 c.c. instead of 0·2 c.c., that is to say, rather less than twice as much as we have used. This five-fold increase in the quantity of fluid gave greatly improved results (*c.f.* also Ritz and Sachs [48]), but it is doubtful whether this increase is of so much value as is claimed for it. It must be pointed out that the results previously obtained by Hauptmann, notably in tabes dorsalis, were very much inferior to the results obtained by many others using

the same small quantities of fluid; and thus the improvement observed by Hauptmann will not be observed to such a marked extent by others. The causes of this diversity are not quite clear, and since we are unacquainted with any full account of Hauptmann's technique, the part played, for instance, by diversity of antigens, cannot be estimated. Some objection has been made to the use of these large quantities, that summation of non-specific anticomplementary action ("Eigenhemmung") is likely to occur, but we have never observed the slightest tendency to "Eigenhemmung" when using cerebrospinal fluid in any quantity.

Quantitative estimations.—In every case the sera and cerebrospinal fluids were estimated quantitatively for their content of reacting substance. It has always been our practice to make the quantitative estimate by varying the amount of serum in the presence of constant amounts of antigen and complement [23]. The maximum quantity of serum used was 0·1 c.c., and this quantity was halved four times, producing the following range: 0·1 c.c., 0·05 c.c., 0·025 c.c., 0·012 c.c., and 0·006 c.c. We have described the result according to the amount which produced complete inhibition of hæmolysis. If complete inhibition may be represented as ++++ in the sense of a complete positive Wassermann reaction, and +++, ++, + stages of inhibition less than complete, we may represent the value of a serum as follows:—

++++
+++-
+++
+
0

This figure implies that 0·1 c.c. and 0·05 c.c. produced complete inhibition; 0·025 c.c. and 0·012 c.c. partial inhibition; while 0·006 c.c. allowed complete hæmolysis. In order to economize space, however, we next reproduced the figure as follows:—

4 (plus signs)
4 ,,
3 ,,
1 ,,
0 ,,

or still more shortly W. R. = 4.4.3.1.0.

In a similar manner in the case of the cerebrospinal fluid we may find W. R. = 4.4.4.4.0, and since we have nearly always tested the serum and cerebrospinal fluid together we should represent this result thus:—

W. R. $\frac{4.4.3.1.0.}{4.4.4.4.0.}$. If the serum was tested alone thus, W. R. $= \frac{4.4.3.1.0.}{-\,-\,-\,-\,-}$

or if the cerebrospinal fluid alone: W. R. $= \frac{-\,-\,-\,-\,-}{4.4.4.4.0.}$

It is often held, particularly in Germany, that the factors involved in the reaction are so complicated and variable that no accurate estimation can be made of two samples of serum unless they are tested together at the same time. Undoubtedly such a method is best, but when the sample is taken from the same patient at different times, it is not applicable. We have always found that our technique is sufficiently exact for quantitative purposes. When each successive quantity of serum is half the former, as suggested, it is quite easy to obtain satisfactory results. We have tested the same material five times, each time with different reagents, and have obtained the same result.

Experiment.—Cerebrospinal fluid (Case 189) unheated and kept sterile in the ice-chest.

June 25, 1913	..	4.4.4.0.0.
July 2, ,,	..	4.4.4.0.0.
July 9, ,,	..	4.4.4.0.0.
July 16, ,,	..	4.4.4.1.0.
July 23. ,,	..	4.4.4.0.0.

Complement.

The complement used was the serum of a guinea-pig. The animal is stunned, and then its throat is cut with a razor, the blood caught in a dish and rapidly transferred to a conical vessel, wherein it is whipped. The blood is next centrifuged and the serum removed. It was always used on the same day.

By the method of freezing, guinea-pig serum may apparently be preserved for several days, but this introduces a factor which is not yet entirely worked out. The serum is placed in a glass capsule and then enclosed in a "thermos" flask with freezing mixture (salt and ice).

Hæmolytic Amboceptor.

This was a sheep-rabbit amboceptor having a minimal hæmolytic dose (M.H.D.), ranging from 0·0003 to 0·0005 c.c. as regards 0·5 c.c of a 5 per cent. sheep's corpuscle suspension, in the presence of 0·1 c.c. of complement diluted 1 in 2.

Whatever the technique of preparation employed, the production of a suitable amboceptor is always a matter of chance and therefore several rabbits should be injected at the same time. When sufficient "titre" has been attained, the animal is bled aseptically, the serum collected and preserved in small capsules. Samples are removed from these capsules for use when required. The amboceptor retains its properties for many months.

Blood Corpuscles.

These were obtained from the sheep. Although the method of collection at the slaughter-house does not entail any aseptic precautions, the blood will remain in a satisfactory condition for three to six days according to the efficiency of the ice-chest in use.

On each test day some of the blood is centrifuged, the serum removed and the deposit washed three times with saline in a dilution of about 6 to 1.

Saline Solution.

Pure crystallized sodium chloride and distilled water were used. The strength was 0·9 per cent.

STANDARDIZATION OF THE REAGENTS.

Since the Wassermann reaction is a measure of the power of the complex antigen-serum to fix complement, it is necessary to standardize all the reagents.

We take as our constant the hæmolytic amboceptor, the strength of which, having once been estimated, does not vary appreciably. It has been stated and appears to be generally held that a "unit" of amboceptor is not a constant quantity, since it is dependent upon the amount of complement present during its estimation. This is indeed the case when dealing with ox corpuscles, but with those of the sheep we have been unable to confirm the statement. With these corpuscles the quantity of complement, presuming that excess is present, does not have a great effect upon the size of a "unit" of amboceptor.

Amboceptor.

Dilutions of amboceptor are prepared in saline in quantities ranging from 0·0001 c.c. to 0·0009 c.c. as follows:—

Measure[1] 0·1 c.c. of amboceptor into 9·9 c.c. of saline and shake: of this dilution place 1 c.c. in 9 c.c. of saline. The amboceptor will then be diluted in 1 in 1,000 and 0·1 c.c. of the dilution will contain 0·0001 c.c. of amboceptor. Thus 0·1 c.c. to 0·9 c.c. of the dilution are measured into 9 test-tubes, and, after the volume in each tube has been brought to 0·9 c.c. with saline, 0·1 c.c. of a 1 in 2 dilution of comple-

[1] Suitable pipettes for all measurements are supplied by Messrs. Baird and Tatlock 14, Cross Street, Hatton Garden, London. They are graduated to the point and the scale is more prolonged than in the case of ordinary measuring pipettes. The same firm supplies the other apparatus mentioned in this paper.

ment is added to each, and, finally, 0·5 c.c. of a 5 per cent. suspension of sheep's corpuscles. The total volume is 1·5 c.c. This mixture is shaken and incubated in the water-bath at 37° C. for twenty minutes. The M.H.D. is then read off and three such doses or three "units" are utilized in the Wassermann test. This standardization should be performed with at least two samples of guinea-pig serum in order to ensure that great excess of complement is present. When once the "titre" is arrived at it is not necessary to re-estimate the strength of the amboceptor for several months.

Complement.

The guinea-pig complement is diluted 1 in 24 with saline, and of this dilution the following quantities are arranged in test-tubes: 0·1 c.c., 0·125 c.c., 0·15 c.c., 0·175 c.c., 0·2 c.c., 0·25 c.c., 0·3 c.c., 0·35 c.c., and 0·4 c.c. The volume is then made up to 1 c.c. with saline and finally 0·5 c.c. of the corpuscle suspension, sensitized in bulk with 3 M.H.D. of amboceptor per 0·5 c.c. (*vide* p. 213) is added to every tube. Incubate for twenty minutes in the water-bath and read the M.H.D. This will usually be 0·2 to 0·3 c.c. of the 1 in 24 dilution. Two and a half M.H.D. are utilized in the Wassermann reaction, but it is not desirable to take a M.H.D. less than 0·175 c.c. of the 1 in 24 dilution and any complement which does not fully hæmolyse in the 0·3 c.c. tube should be discarded. The standardization of the complement must be carried out every day with the actual suspension of corpuscles in use.

The dilution of the complement is so arranged that the requisite amount for the Wassermann reaction (2½ M.H.D.) is contained in 0·5 c.c.

On calculation it will be found that if the M.H.D. of the 1 in 24 dilution is 0·175 c.c., 0·2 c.c., 0·25 c.c., or 0·3 c.c., it will be necessary to use in the test 0·5 c.c. of a 1 in 27, 1 in 24, 1 in 19, or 1 in 16 dilution respectively.

Antigen.

As already stated, various samples of heart-cholesterin antigen do not differ in antigenic value, so long as the methods of preparation are identical. In practice, therefore, it is quite unnecessary to standardize various samples. When making the antigen for the first time, however, it will be desirable to control the technique of preparation by standardization. The method adopted is to standardize according to anticomplementary effect in the absence of syphilitic serum. As

is well known certain of the constituents of the antigen have an inherent destructive effect upon complement, quite apart from the power of "fixation" in the presence of syphilitic serum. This "anticomplementary" effect is the chief factor which determines the amount of antigen to be used in the test, since too great a quantity would leave too little complement free to participate in the specific reaction. The anticomplementary action of many antigens varies in different samples, and thus the quantity selected for use will vary without regard to the true "antigenic" value of the extract. In the case of our antigen, however, the anticomplementary action of different samples is equal [28], as also is the antigenic, and thus standardization by anticomplementary effect will always furnish a reagent of constant value. We determine the "completely inhibiting dose" of the antigen and then select a certain fraction of this which will give a sufficient margin of safety. We therefore utilize in the reaction one quarter of that quantity which will alone produce complete inhibition of hæmolysis after being incubated for one hour with the complement in the air incubator. It will be found that twice this quantity, that is one half of the "completely inhibiting dose" will just permit of complete hæmolysis. With our own methods of preparation the quantity of antigen to use is 0·5 c.c. of a 1 in 15 dilution in saline solution as shown below.

Experiment showing the Anticomplementary Action of the Heart-cholesterin antigen.

Antigen—3 parts of heart + 2 parts of cholesterin, diluted	Quantity of dilution used	Complement 2½ M.H.D.	Result
1 in 10	0·5 c.c.	0·5 c.c.	0
1 in 8	,,	,,	0
1 in 6	,,	,,	+ +
1 in 4	,,	,,	+ + + +
1 in 3	,,	,,	+ + + +
1 in 2	,,	,,	0

(+ + + + = complete inhibition. 0 = complete hæmolysis.)

0·5 c.c. of the 1 in 4 dilution is the smallest amount which gives complete inhibition, therefore 0·5 c.c. of a 1 in 16 dilution should be used. Actually we utilize 0·5 c.c. of a 1 in 15 dilution. The strongest solution (1 in 2) produces hæmolysis, owing to the hæmolytic action of soaps and alcohol. It will be noticed that double the test quantity, i.e., 0·5 c.c. of a 1 in 8 dilution permits of complete hæmolysis.

Serum or Cerebrospinal Fluid.

As already stated, 0·1 c.c. of heated serum is the maximum quantity used, while 50 per cent. dilutions are prepared from it. The method is as follows: 0·1 c.c. is measured into the first tube by the method of Donald [11], using drops. Glass pipettes are calibrated by passing them through particular holes in a wire gauge plate until they are held firmly; they are then cut off flush with the plate and it is found that pipettes made in the same hole will drop the same number of drops per cubic centimetre when the instrument is held in the same position. We use hole No. 53 in the Stubbs wire gauge plate, and find that a pipette made in such a manner will furnish 0·1 c.c. of serum in four drops when held vertically. Thus our quantities of serum are prepared as follows:—

0·1	c.c.	= 4 drops	
0·05	,,	= 2 ,,	
0·02	,,	= 1 ,,	
0·012	,,	= 4 ,,	of a 1 drop in 8 drops dilution
0·006	,,	= 2 ,,	,, ,, ,, ,,

For measuring cerebrospinal fluid, we use the same pipette, although this introduces a trifling error, owing to the different surface tension of the two fluids:—

0·2	c.c.	= 8 drops	
0·1	,,	= 4 ,,	
0·05	,,	= 2 ,,	
0·02	,,	= 1 ,,	
0·01	,,	= 4 ,,	of a 1 drop in 8 drops dilution

We do not in any case trouble to make the total volumes equal with saline, since the difference in bulk is of no consequence.

PRELIMINARY ARRANGEMENTS FOR THE TEST.

The requisite quantities of the reagents for the day's tests are calculated as follows:—

Assume that 20 sera are to be tested. Each serum will require five antigen tubes and one control without antigen—six tubes in all. The sensitized emulsion of corpuscles is first arranged: $6 \times 20 = 120$ tubes required = 60 c.c. (0·5 c.c. per tube). This is made up as follows:—

Amboceptor 3 M.H.D. per tube = 0·0009 × 120 = (M.H.D. = 0·0003 c.c.)	0·108	c.c.
Corpuscle deposit	3·00	,,
Saline solution	56·90	,,
	60·308	,,

This will provide a 5 per cent. corpuscle suspension, every 0·5 c.c. of which will contain the correct quantity (3 M.H.D.) of amboceptor per tube. The amboceptor is added first to the saline and then the corpuscles. Shake thoroughly. In practice it is usual to make up a small excess of all reagents.

The next operation is to standardize the complement against this sensitized suspension, and while this is proceeding the antigen dilution is prepared as follows :—

If twenty sera are to be tested, 100 antigen tubes will be required or 50 c.c. of antigen (0·5 c.c. per tube). The mixture of heart-extract and cholesterin is diluted 1 in 15. Therefore $\frac{50}{15} = 3{\cdot}3$ c.c. of the combined antigen will be required, or 1·98 c.c. of heart + 1·32 c.c. of cholesterin. The dilution is therefore made as follows :—

Heart-extract	1·98 c.c.	Mix	Mix rapidly.
Cholesterin solution	1·32 ,,		
Saline	46·70 ,,		
	50·00 ,,		

The heart-extract and cholesterin are mixed together in a large test-tube and the requisite quantity of saline is poured in rapidly. It is now found that 0·25 c.c. of the 1 in 24 dilution of complement is the minimal haemolytic dose, and therefore 0·25 × 2·5 = 0·625 c.c. of the 1 in 24 dilution should be used in the test or 0·5 c.c. of a 1 in 19 dilution. Fifty cubic centimetres of this (0·5 c.c. per tube) will be required for the antigen tubes, thus 2·6 c.c. of complement added to 47·4 c.c. of saline should be prepared. The 50 c.c. of diluted antigen is added to the 50 c.c. of diluted complement *just before use* and 1·0 c.c. of the mixture is placed in every tube requiring antigen. Twenty control tubes without antigen also require complement; in this case, however, the complement should be diluted 1 in 38 in order to make up the bulk in the absence of antigen. Twenty tubes require 20 c.c. of 1 in 38 complement, that is 0·52 c.c. of complement + 19·48 c.c. of saline; 1 c.c. of this is added to every control tube.

The Test.

Suitable test-tubes measure 4 × $\frac{5}{8}$ in. (10 × 1·6 cm.), and are made of stout glass. They are arranged in metal racks holding twenty-four, in four groups of six. Each row of six belongs to one patient, the first five containing antigen and the sixth being a control. It is desirable that all tubes, both in the front row and also in the back be viewed and read

off from one side only, i.e., the front, which should be indicated by a mark. If the left and right hand of the rack is thus kept constant there is less liability to confusion when filling in the reagents.

Having measured in all sera first and then the complement with and without antigen, the racks are shaken and put into the air incubator at 37° C. for one hour.

It has been stated that the fixation of the complement in the first stage of the Wassermann reaction proceeds best at a temperature of 37° C. in the water-bath, while others claim that the temperature of the ice-chest is more satisfactory. We have been unable to detect any improvement by these methods over incubation in air at 37° C.; on the contrary, we have found them somewhat inferior. It will be understood that fluid in an air incubator at 37° C. does not reach this temperature for a long time, and therefore such a method really corresponds to incubation at room temperature for much of the period. Thomsen and Boas [57] have shown that the statements regarding improvement in the ice-chest are based upon experimental errors, and have found that fixation proceeds best in most cases at room temperature and in a few at 37° C. in the water-bath. They therefore suggest three-quarters of an hour fixation at room temperature followed by a quarter of an hour at 37° C. in water. Probably the method used by us produces similar results.

SCHEMA OF THE TEST.

Tube	1	2	3	4	5	6	Controls 7	8	9
	c.c.	c.c.	c.c.	c.c.	c.c.	c.c.	c.c.	c.c.	c.c.
Serum	0·1	0·05	0·025	0·012	0·006	0·1	—	—	—
or									
Cerebrospinal fluid ..	0·2	0·1	0·05	0·025	0·012	0·2	—	—	—
Antigen .. 0·5 c.c.	1·0	1·0	1·0	1·0	1·0	—	1·0	—	
Complement 0·5 „									
Saline .. 0·5 c.c.	—	—	—	—	—	1·0	—	1·0	—
Complement 0·5 „									
Incubate for one hour at 37° C. in air.									
Sensitized corpuscles..	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·5	1·5

Incubate for twenty minutes at 37° C. in water. Then read the results, or allow to stand for one hour at room temperature, without shaking.

After fixation the sensitized emulsion is added and the tubes are shaken. The racks are then placed in water at 37° C. The water-

bath is economical of time, since twenty minutes is about equivalent to sixty minutes in the air incubator. After the lapse of twenty minutes the racks are taken out and the results read off, or, to facilitate the recognition of small degrees of hæmolysis, they are first allowed to stand for one hour for the corpuscles partially to settle down.

No special provision is made for known syphilitic and non-syphilitic controls because such are always present in a large series.

It will be noticed that our "controls" differ from those used in the "original technique."

According to the original account it was necessary to show that twice the test quantity of antigen permitted complete hæmolysis. We use only one dose of antigen as control, nevertheless from long experience we have found that twice our antigen dose will permit of hæmolysis, and since our antigen, unlike syphilitic liver-antigens, is not variable, there is no danger in this procedure. Further, the double antigen control is now given up by most followers of the original method. It is the practice to use a larger quantity of antigen in the test, and this quantity will not permit of hæmolysis in double dose. Thus it is clear that so far as antigen is concerned our technique is "safer."

Further, it is the general practice to control the "Eigenhemmung" of the serum and cerebrospinal fluid by "double dose" controls. As we have already pointed out, however, this is quite unnecessary in the case of the cerebrospinal fluid. It is true that serum shows more "Eigenhemmung" than cerebrospinal fluid, but in practice when dealing with fresh, sterile, and quickly heated serum, "Eigenhemmung" is very seldom seen. We control the phenomenon by observing the velocity of the reaction, that is to say, if we find a case in which the single dose of serum does not rapidly hæmolyse, we look upon the result with suspicion.

Interpretation of the Result.

In the great majority of cases it will be found that either complete hæmolysis has occurred in every tube thus: $\frac{0.0.0.0.0.}{\cdot\ \cdot\ \cdot\ \cdot\ \cdot}$, or in one or more tubes there is a complete inhibition, thus: $\frac{4.1.0.0.0.}{\cdot\ \cdot\ \cdot\ \cdot\ \cdot}$. A few cases will, however, be found in which inhibition is present in the first tube, although it is not complete: $\frac{3.0.0.0.0}{\cdot\ \cdot\ \cdot\ \cdot\ \cdot}$; $\frac{2.0.0.0.0.}{\cdot\ \cdot\ \cdot\ \cdot\ \cdot}$ or $\frac{1.0.0.0.0}{\cdot\ \cdot\ \cdot\ \cdot\ \cdot}$, and the question arises as to whether these cases are to be reported positive or not.

The figure $\underline{3.0.0.0.0.}$ represents from a trace to 25 per cent. of hæmolysis.

$\underline{2.0.0.0.0.}$ „ „ 25 to 50 per cent. „ „

$\underline{1.0.0.0.0.}$ „ „ 50 to 75 per cent. „ „

While it is safer to restrict the term "positive reaction" to complete inhibitions in the first tube $\underline{4.0.0.0.0.}$, nevertheless, in practice, we also include slight degrees of hæmolysis up to 25 per cent. under this heading, $\underline{3.0.0.0.0}$, and have not observed any error in diagnosis by so doing; this may be said to be the general practice with regard to the Wassermann test. When, however, the greater degrees of hæmolysis 2.0.0.0.0. or 1.0.0.0.0. are considered, it is necessary to take into account two different conditions.

Firstly, whether it is known to the tester that the serum has reacted positively in his hands on a former occasion, or whether he is ignorant of the antecedents of the case. In general diagnostic work, when nothing is known about a serum, it would be extremely unwise to pay any attention to results shown as 2.0.0.0.0. or 1.0.0.0.0., since there are several non-syphilitic conditions which may give this amount of inhibition, notably some cases of febrile tuberculosis, or pneumonia. If, however, the serum is known to have been positive on a former occasion, it is of importance to record these slight results, since they then indicate that the syphilitic patient has not yet a completely negative reaction. They will, of course, be observed constantly in all cases of syphilis under treatment at some period, and no patient can be looked upon as "cured" so long as such a result is obtained.

We therefore hold that from the strict serological standpoint 2.0.0.0.0. or 1.0.0.0.0. have no diagnostic significance, but nevertheless, may be important from the point of view of treatment.

CHAPTER II.—THE OCCURRENCE OF THE WASSERMANN REACTION.

Introduction.

The diagnostic value of a biological test depends largely upon the frequency with which a positive result may be expected. Some reactions when positive may be decisive, but they may be so seldom positive that a great deal of their practical utility is lost. The value of a test is much increased if it is found to be positive so frequently in undoubted examples of the particular condition that a negative result assumes a certain value.

Thus the diagnostic value of the Wassermann reaction depends to a large extent upon the constancy of its occurrence in syphilis. If it is admitted that a positive result is, within limits, undoubtedly indicative of syphilis, it does not of course follow that a negative result will exclude this disease. Numerous cases of undoubted syphilis are known in which the reaction has been negative for reasons explicable or inexplicable. It therefore is clear that a negative reaction does not exclude syphilis; such a result merely introduces a certain improbability into this diagnosis, and the improbability will be greater or less according to the frequency with which negative reactions are usually obtained in cases of syphilis. A negative reaction in acute secondary syphilis is extremely rare, and therefore a diagnosis of secondary syphilis in spite of this result will be extremely improbable. On the other hand, negative results are not so uncommon in tertiary syphilis and therefore such a diagnosis may be made in the face of a negative reaction with greater probability than in secondary syphilis.

This method of reasoning, however, presumes that the results obtained by different apparently competent persons are of equal value; but a short study of the literature is sufficient to show that this is not the case; thus one investigator may find 60 per cent. of cases of tertiary syphilis positive, while another may find 100 per cent. positive. It is clear, therefore, that the average results obtained by the particular tester must be known before the value of his negative result is fully appreciated.

The reputation of the Wassermann reaction depends upon two factors, firstly, the accuracy of the technique employed, and secondly, the accuracy of the clinical diagnosis on which are calculated the percentage results of the serologist.

It is always found that the poorest results are obtained in general diagnostic work, when the sera are sent for examination by a number of clinicians of varying experience and when the correctness of the diagnosis is not open to investigation. The best results, on the other hand, are obtained when the sera emanate from one source of undoubted excellence and in particular when the diagnosis is revised after further investigation of the case along lines suggested by the serological result.

Owing to the above considerations an examination of the literature does not throw much light upon the question of the occurrence of the reaction. It is usually found that if the technique is fully described there is no reference to the accuracy of the clinical diagnosis, while, if the details of the cases are entered into, the serological details are given in an entirely uncritical manner.

In order to avoid this error as far as possible in the present case, we always append to the serological result a reference to a full clinical study of the patient, and, on the other hand, we have given a full account of the methods by which we have arrived at this result.

The Occurrence in General Diagnostic Work.

As a general index of the results obtained by our particular technique, the following figures may be quoted. They represent the routine tests carried out in cases of general syphilis excluding nervous conditions. In every instance the diagnosis was described as being "clinically certain," and in the great majority this was the personal view of Dr. J. H. Sequeira, dermatologist to the London Hospital.

Antisyphilitic treatment had not been practised to any great extent.

Cases of Active Syphilis described as "clinically certain," tested between January, 1912, and February, 1913.

	Total	Positive	Negative	Positive per cent.
Primary syphilis	33	31	2	93
Secondary syphilis	109	108	1	99
Tertiary syphilis	195	190	5	97
Congenital syphilis	35	35	0	100

These results are comparable with those published by Boas, and demonstrate the very high degree of accuracy attained by the Wassermann reaction at the present time. It is clear that a diagnosis of active syphilis in the absence of a positive reaction will require very special support before it can be considered probable. As regards the specificity of the reaction, we have only found one non-syphilitic individual giving a positive result in recent years—a case of acute malaria twenty-four hours after a rigor. Other cases of malaria, leprosy, &c., have given negative reactions. We have had no experience of scarlet fever recently, though formerly we have described fleeting positive results.

The Occurrence in Syphilis of the Central Nervous System.

Under this heading we discuss the incidence of the Wassermann reaction not only in cases of cerebrospinal syphilis but also in the so-called "parasyphilitic" conditions. The classification follows the usually accepted clinical demarcations, but it must be stated at once that such demarcations are not absolute. There are so many instances

of transitional forms not only between dementia paralytica and tabes dorsalis, but also between these "parasyphilitic" states and admitted "cerebrospinal syphilis," that too much importance should not be directed to exceptions to any "rules" which may be evolved.

The reports in the literature on the Wassermann reaction in neurological cases are extremely variable, and frequently refer only to asylum patients. Relatively little attention has been directed to the study of nerve lesions as found in general hospitals.

We have classified our results under the following headings:—

(1) Dementia paralytica, including the transitional forms of tabo-paralysis.

(2) Tabes dorsalis, including those cases associated with optic atrophy, amyotrophy, and Erb's degeneration.

(3) Cerebrospinal syphilis, subdivided into two groups:—

(*a*) Those cases in which there is clinical evidence of a lesion of the spinal cord with or without involvement of the brain.

(*b*) Those cases in which the brain only appears to be affected.

(1) *Dementia Paralytica, &c.*

According to an examination of the earlier literature (1908-1910) already published by us [25], 98 per cent. of cases of dementia paralytica give a positive reaction in the serum, and 85 per cent. in the cerebrospinal fluid. Although these figures denote a high proportion of cases positive, the results obtained by the best methods at the present time give a considerably higher proportion, especially as regards the cerebrospinal fluid. Thus Plaut [42] describes two negative among 320 sera, practically 100 per cent. positive; while in 276 cerebrospinal fluids nine were negative, or 96 per cent. positive.

Being confined entirely to hospital cases, our results in this section are relatively few. Both the serum and cerebrospinal fluids were positive in twenty cases. From such findings it is clear that the sera in these conditions almost always give a positive result, and the cerebrospinal fluid is negative as an abnormality only. When it is reported, as for instance by Nabarro [34] or by Kirchberg [18], that cases of dementia paralytica frequently give a negative reaction, it must be supposed that some abnormal factor is operating in the series to account for this result.

If the following table be studied, it will be noticed that the cerebrospinal fluid very seldom, if ever, gives a stronger reaction than the serum, in particular when it is remembered that the fluid is used in

double quantity and is unheated; thus, since it nearly always reacts less strongly, it will tend to give a negative reaction in rare cases more often than the serum, as is indicated by the published figures. Another factor which probably ensures a more frequent negative reaction in the cerebrospinal fluid is an incorrect diagnosis. It will be allowed that if it is possible to confuse certain cases of syphilitic vascular disease with dementia paralytica, this will account for a negative reaction in the cerebrospinal fluid, while the serum will still be positive, since both conditions are syphilitic. In this connexion the work of Candler [9] is of great interest. In 1909, with Henderson Smith, he tested the cerebrospinal fluid of a number of "general paralytics"; seventy-five of these have now died, and have been examined. Eight cases gave negative reactions during life, and thus only 89 per cent. were positive; but at the autopsy it was found that six of the negative cases were not "general paralytics"; thus in actual fact they had obtained a percentage of 97 positive. This example not only illustrates the fallacies associated with the statistical method in medicine, but also the great difficulty encountered in the diagnosis of dementia paralytica even among the most expert.

THE INCIDENCE OF THE WASSERMANN REACTION IN DEMENTIA PARALYTICA, &c.

No. of case		Result of first examination		No. of case		Result of first examination	
(Juvenile)	16	serum	4.4.4.4.4.		96	serum	4.4.4.4.3.
		cs.f.	4.4.4.4.4.			cs.f.	4.4.4.4.2.
	17		4.3.0.0.0.		108		4.4.4.4.0.
			4.2.0.0.0.				4.4.4.4.3.
	20		4.4.4.3.1.	(Juvenile)	109		4 4.4.4.4.
			4.4.4.4.1.				4.4.4.4.3.
	32		4.4.4.2.1.		119		4.4.4.4.4.
			4.4.4.3.2.				4.4.4.4.4.
	33		4.4.4.4.4.		132		4.4 0.0.0.
			4.4.4.0.0.				4.4.4.0.0.
	80		4.4.4 3.2.		152		4.4.4.3.1.
			4.4.4.4.4.				4.4.4.0.0.
	81		4.4.4.4.4.		165		4.4.3.2.1.
			4.4.4.4.4.				4.4.4.4.0.
	90		4.4.4.4.2.		169		4.4.4.4.4.
			4.4.4.4.0.				4.4.4.4.4.
	93		4.4.4.4.0.	(Juvenile)	197		4.4.4.4.4.
			4.4.1.0.0.				4.4.4.2.0.
	95		4.4.4 3.2.		214		4. - - - -
			4.4.4.3 2.				4.4.4.4.4.

(2) *Tabes Dorsalis, &c.*

In a former study of the literature (1907-1909) we found that 63 per cent. of cases of tabes dorsalis gave a positive reaction in the serum and 32 per cent. in the cerebrospinal fluid. These figures indicate that a positive reaction in both fluids is less constant than in dementia paralytica and that the cerebrospinal fluid fails to give the reaction in a large number of cases. Variety of technique, however, is responsible for divergent results to a larger extent than in dementia paralytica; thus in 1909 Nonne [38] described 50 per cent. positive in the cerebrospinal fluid, while in 1911 [39], he gave 5 to 10 per cent. only positive when using the ordinary test quantities, though with the increased amounts of the "Auswertungsmethode," he obtained practically 100 per cent.

The literature dealing with tabes dorsalis is much smaller than that of dementia paralytica, and in many instances the serum only has been examined.

Our results have been as follows:—

THE INCIDENCE OF THE WASSERMANN REACTION IN TABES DORSALIS, &c.

No. of case	Result of first examination		No. of case	Result of first examination	
13	serum	4.4.3.2.1.	83	serum	2.0.0.0.0.
	cs.f.	4.4.4.1.0.		cs.f.	0.0.0.0.0
14		4.4.4.4.4.	89		4. - - - -
		4.4. - - -			4. - - - -
23		4.4.4.4.4.	112		4.4.4.4.1.
		4.3.0.0.0.			4.4.4.4.1.
27		4.4.4.3.0.	117		2.0.0.0.0.
		3.1.0.0.0.			4.4.4 4.1.
30		4.1.0.0.0.	131		4.3.2.1.0.
		4.4.4.4.0.			4.4.4.3.1.
37		4.4.2.0.0.	142		4.4.4.0.0.
		4.4.3.1.0.			4.4.4.0.0.
46		4.4.4.4.3.	143		4.4.4.4.0.
		3.0.0.0.0.			4.4.1.0.0.
55		4 3.1.0.0.	144		0.0.0.0.0.
		4.4.3.1.0.			0.0.0.0.0.
56		4.4.4.4.1.	145		4.3.2 0.0.
		4.4.4.4.1.			4.4.3.3.0.
58		4.3.1.0.0.	150		4.4.4.4.2.
		4.4.4.1.0.			4.4.3.0.0.
67		4.3.2.0.0.	186		4.4.3.0.0.
		4.4.4.0.0.			4.4.3.0.0.
70		4.4.4.2.0.	200		4.4.4.4.3.
		4.3 0.0.0.			4.4.4.4.4.

Of the twenty-four cases shown above, two were negative in both serum and cerebrospinal fluid (Nos. 83 and 144), while No. 117 was negative in the serum and positive in the cerebrospinal fluid.

On reference to the accounts it will be found that the disease in the two negative cases (Nos. 83 and 144) was quite stationary, although No. 83 had recently developed a Charcot knee. This condition is, however, usually looked upon as trophic and at any rate does not indicate the presence of an active syphilitic lesion. It is probable that in this case the syphilitic process was practically extinct, and in support of this view is the fact that no exacerbation of the reaction occurred after an injection of neo-salvarsan. As regards No. 144 the condition had been stationary for two years and much anti-syphilitic treatment had been applied. In his case, however, the syphilitic process cannot be looked upon as extinct since an injection of neo-salvarsan produced a well-marked "provocative reaction."

This "provocative reaction" was not obtained in the cerebrospinal fluid, and from this fact we conclude that the syphilitic focus which gave rise to it was not "tabetic" since in this case we should have expected some "leakage" into the cerebrospinal fluid.

On the other hand, the negative reaction in the serum of No. 117 and the positive in the cerebrospinal fluid suggests that active lesions in this case were situated in the central nervous system only. The case further supports our contention that the cerebrospinal fluid is relatively stagnant and that substances tend to accumulate in it without passing into the general circulation along the "lymphatic" communications usually described.

The number of cases described is small (24), but it is seen that three negative reactions occurred in the serum and two in the cerebrospinal fluid. These results are consistent with a positive percentage in the serum of 88 and 92 in the cerebrospinal fluid. In tabes dorsalis, however, it is clear that the figures are complicated by factors which probably do not affect dementia paralytica so much. Natural variations in the intensity of the disease or the effects of treatment bear upon the serological result as already clearly shown by Boas [5] in the case of serum. Thus when the reaction is used as a help in the diagnosis of tabes dorsalis, it is essential to notice the activity or otherwise of the disease and also the occurrence of anti-syphilitic treatment, and further, since the reaction may be negative in the serum and positive in the cerebrospinal fluid, it is not enough to examine the former alone.

As regards the strength of the reaction in tabes dorsalis, in particular

in the cerebrospinal fluid, it is seen that this on the whole tends to be less than in dementia paralytica, but if it is admitted that weak reactions are common (*c.f.* Nos. 23, 27, 46, 70), it must also be allowed that strong reactions are also frequent. We cannot altogether agree with Nonne [39] therefore when he states that a strong reaction in the cerebrospinal fluid suggests a "great probability of paralysis or tabo-paralysis" and "much less often" of a pure tabes. In our opinion the difference is too inconstant to be of diagnostic importance. Nevertheless a feeble reaction in the cerebrospinal fluid is considerably more common in tabes dorsalis than in dementia paralytica as is also the occurrence of a positive reaction in the cerebrospinal fluid associated with a negative in the serum. In fact it is probable that this combination never occurs in dementia paralytica.

(3) *Cerebrospinal Syphilis.*

The occurrence of the Wassermann reaction in cerebrospinal syphilis has presented problems of the greatest interest.

In the early days of the reaction as applied to neurology, it was generally held that it was not found in the cerebrospinal fluid of these cases and, indeed, a positive reaction in this fluid was held to be strong evidence of "parasyphilis"; thus Mott introduced and still supports a theory in connexion with "parasyphilis" which utilizes this supposed fact in the argument. He states [33]: "Again the observations of Dr. Topley on my hospital cases of cerebral and cerebrospinal syphilis, compared with tabes and general paralysis, entirely conform to Plaut's results. The fluid in cerebrospinal syphilis did not give a positive reaction."

According to Plaut [44] "Both in lues cerebri and in lues spinalis the negative reaction is the rule. . . . This result is found equally in all forms of the disease." Nonne [39] also gives as a typical result in the fluid of cerebrospinal syphilis:—

"(*a*) Originalmethode (0·2 c.c.) positiv in ca. 10 Proz.

"(*b*) Höhere Liquormengen fast stets positiv."

This remark dealing with the larger quantities of test fluid, refers to the "Auswertungsmethode" of Hauptmann and Hössli, which is now generally used in Germany. Instead of 0·2 c.c. of cerebrospinal fluid in a total volume of 3 c.c. in the fixation stage as required by the "original method," this modification utilizes increasing quantities up to 1·0 c.c., and by these means the reaction is found to be almost constant

in cerebrospinal syphilis, although this effect is obtained only with the larger quantities.

The results obtained by us in these cases differ in certain respects from those already described. For the purposes of classification we have divided them into two groups. In the first are found those in which the spinal cord was affected, either alone or together with the brain, while in the second those in which the spinal cord was apparently not affected.

INCIDENCE OF THE WASSERMANN REACTION IN CEREBROSPINAL SYPHILIS.

A—Cases in which the cord was apparently affected.

No. of case	Result of first examination	No. of case	Result of first examination
3	serum 4.4.4.4.4.	102	serum 4.4.0.0.0.
	cs.f. 4.4.4.3.2.		cs.f. 4.3.1.0.0.
7	4.4.4.4.4.	106	4.4.4.4.4.
	0.0.0.0.0.		4.4.0.0.0.
10	4.4.4.1.0.	114	4.2.0.0.0.
	4.1.0.0.0.		4.4.4.4.4.
19	4.4.4.4.4.	120	4.2.0.0.0.
	4.4.4.3.2.		4.3.2.0.0.
26	4.4.4.4.4.	125	4.4.4.4.4.
	4.4 4.0.0.		4.4 4.4.3.
36	4.4.4.4.2.	134	4.4.4.4.0.
	4.4.1.0.0.		4.4.4.4.4.
45	4.4.4.4.4.	146	4.4.4.4.4.
	4.4.4.4.4.		4.4.4 4.2.
54	4.4.4.1.0.	147	0.0.0.0.0.
	0.0.0.0.0.		4.4.1.0.0.
59	4.4.4 4.4.	175	4.4.4.4.4.
	4.4.4.4.3.		4.4.4.4.2.
60	4.4.4.4.4.	177	4.4.4.4.4.
	4.4.3. - -		4.4.4.4.0.
64	4.3.2.0.0.	182	0.0.0.0.0.
	4.4.4.3.1.		0.0.0.0.0.
74	4.4.4.4.3.	189	4.4. - - -
	4.4.4.3.1.		4.4.4.0.0
77	4.4.4.4.4.	199	4.4.4. - -
	4.4.4.3.0.		4.4.4.4.0.
86	4.4.3.3.0.	201	4.4.4.4.4.
	4.4.4.4.0.		4.4.4.4.4.
91	4.4.3.0.0.	202	4.4.4. - -
	4.4.4.1.0.		4.3.0.0.0.
94	1.0.0.0.0.	217	4 4.4.4.0.
	4.4.4.3.0.		4.4.4.4.0.
97	4.4.4.4.4.		
	0.0.0.0.0.		

B—Cases in which the Brain only was affected.

No. of case	Result of first examination	No. of case	Result of first examination
15	serum 4.4.4.4.0. cs.f. 0.0.0.0.0.	123	serum 0.0.0.0.0. cs.f. 4.4.2.0.0.
39	4.4.4.4.4. 0.0.0.0.0.	128	4.4.4.4.4. 4.1.0.0.0.
44	3.2.0.0.0. 0.0.0.0.0.	133	4.4.4.4.4. 0.0.0.0.0.
53	4.4.4.0.0. 0.0.0.0.0.	148	0.0.0.0.0. 4.2.0.0.0.
61	4.4.4.4.4. 0.0.0.0.0.	149	4.4.4.4.2. 0.0.0.0.0.
62	4.4.2.0.0. 0.0.0.0.0.	156	4.4.4.4.2. 0.0.0.0.0.
73	4.4.4.4.0. 0.0.0.0.0.	158	4.4.4.4.4. 0.0.0.0.0.
85	4.4.4.4.4. 0.0.0.0.0.	159	4.4.4.3.0. 4.4.4.4.1.
92	4.4.4.4.0. 0.0.0.0.0.	161	3.2.0.0.0. 0.0.0.0.0.
104	4.4.4.4.3. 0.0.0.0.0.	170	4.4.4.4.4. 4.4.0.0.0.
107	4.4.3.1.0. 4.2.0.0.0.	183	4.4.4.4.4. 4.4.4.4.4.
110	0.0.0.0.0. 0.0.0.0.0.	204	4.4.4.4.1. 0.0.0.0.0.
111	4.3.1.0.0. 0.0.0.0.0.	205	4.1.0.0.0. 0.0.0.0.0.
122	4.4.4.4.4. 0.0.0.0.0.		

On analysing these figures, it will be found that the number of cases in Group A (cord affected) is thirty-three. The serum gave a positive reaction in all but three cases, Nos. 94, 147 and 182. As regards the last case (No. 182) this negative result is the natural consequence of treatment. The negative reaction in the serum of No. 94 is interesting, being associated with a positive in the cerebrospinal fluid. The case presents several points of similarity with No. 123. In both the examination was made very soon after the onset of the nervous symptoms, and in both the serum subsequently became positive. The results appear to indicate that the syphilitic process was confined to the nervous system, the rest of the body being free as in the case of the so-called "nerve relapses" of the literature. This being the case, the products of the inflammation are first detected in the cerebrospinal fluid and only at a later date do they

appear in the blood. If the treatment of the patient is sufficiently intensive, the positive reaction in the serum is only transient.

No. 147 is clinically a very complex case, and the significance of the negative reaction is not clear.

Turning to the cerebrospinal fluids it is seen that four of the thirty-three cases gave a negative reaction. In three of these (Nos. 7, 54, and 182) intensive treatment had been applied, while the other negative case (No. 97) is on the border line between Groups A and B. This case (No. 97) is included among those in which the spinal cord appeared to be affected, on the grounds that the patient exhibited a hyperæsthesia of one thoracic segment which subsequently was associated with muscular wasting. That the lesion was extremely trivial is shown by the presence of only 1 cell per cubic centimetre in the cerebrospinal fluid.[1]

Referring to the effect of treatment shown above, it is necessary to state that in statistics of cerebrospinal cases it is essential to note the existence of anti-syphilitic treatment, since, as will appear later, the reaction in the cerebrospinal fluid in such cases is extremely sensitive to treatment and may rapidly become negative, thus confusing the issue.

Due attention being paid to this question and also to the triviality of the signs in No. 97, it is clear that a positive reaction in the cerebrospinal fluid of patients in whom the spinal cord is affected is a constant phenomenon, as constant even as in dementia paralytica.

Turning to those cases in which the cord was apparently not affected (Group B) twenty-seven in number, it will be seen that three gave a negative reaction in the serum (Nos. 110, 123, and 148), and twenty a negative in the cerebrospinal fluid. No. 123 had been treated originally by salvarsan and the positive reaction in the fluid may be looked upon as a "nerve relapse," as described in the literature; that is, a slight meningo-encephalitis occurring in an almost completely sterilized individual. Since the initial lesion is in the meninges, the positive reaction is detected in the cerebrospinal fluid before it appears in the serum. As regards Nos. 110 and 148, these are both cases of hemiplegia due to cerebral thrombosis, and it is commonly found that such tend

[1] We are much indebted to Dr. R. Donald, who made all the cell enumerations mentioned in this work. The method of counting utilizes Donald's technique of measured drops already referred to [11], and not only ensures greater accuracy than a counting chamber but also provides permanent preparations. A small drop of known capacity is deposited on a slide, fixed *in situ* by a superimposed collodion film, stained and counted through by means of a mechanical stage. (*Vide* R. Donald, "Folia Hæmatologica," *Archiv.* [in the press].)

to give feeble or negative reactions in the serum. It is clear that a slight thrombotic lesion outside the nervous system might not attract notice, while in the nervous system it will produce marked clinical symptoms. It is possibly this factor which brings a trivial lesion with its accompanying trivial reaction to the notice of the neurologist. In the cerebrospinal fluid also the purely thrombotic cases seldom give a positive reaction, as already noticed by Assmann [2 and 3] and Plaut [44], and this result is no doubt largely due to the fact that the main inflammatory process is confined to the endothelium of the larger vessels, and thus does not affect the pia and occasion an exudate into the sub-arachnoid space. The same factor may also perhaps produce a negative reaction in the cerebrospinal fluid even when the cord is affected by a thrombotic lesion. No. 104, included in Group B, may, on the strength of a slight sphincter lesion, be looked upon as belonging to Group A, the negative reaction in the cerebrospinal fluid being accounted for by a thrombotic lesion.

In contradistinction to Group A, the cerebrospinal fluid of cases in Group B relatively seldom gives a positive reaction; there were seven instances only in twenty-seven. Thus, as a rule, the cerebrospinal fluid in purely cerebral cases is negative. The exceptions to the rule, those cases giving a positive reaction in the cerebrospinal fluid, may now be considered. In Nos. 107, 123, 128, and 170, it will be observed that the condition was recent.

No. 148 gave a slight positive reaction but, although at the time of examination he had no sphincter trouble, nevertheless during the original attack this was present, suggesting that there was some affection of the spinal cord.

In No. 159 the reaction of the cerebrospinal fluid is strong although there is little evidence of a lesion of the cord. It is, however, probable that the syphilitic process extended along the medulla, and thus, perhaps, the case should have been included in Group A.

The final example of a positive reaction in the cerebrospinal fluid is No. 183, which resembles No. 59, included in Group A. Both cases differ from all others in being examples of acute encephalitis or perhaps more accurately of acute encephalo-myelitis. The spinal cord was probably involved, but the condition was so recent that no localizing signs had appeared at the time of examination.

It will be seen from the cases described that there is much justification for the division into the two Groups A and B. The cerebrospinal fluid in Group B is almost always negative, and only when the lesion is quite recent is a slight positive reaction found.

The explanation of the difference in the reaction in these two groups probably lies in the fact that the sample of the cerebrospinal fluid examined is derived from the lumbar region. As we have pointed out elsewhere, the sub-arachnoid space in the brain is small, and in fact merely represents a capillary space; there is also no obvious flow of fluid from the brain to the lumbar region and thus constituents of the cerebral fluid will diffuse but slowly into the spinal fluid. It is therefore clear that Wassermann bodies poured into the cerebrospinal fluid directly from a lesion of the spine will be detected more readily than bodies diffusing slowly from the brain.

The strength of the Wassermann reaction in cerebrospinal syphilis (Group A) appears from our tests to be very strong and does not in any way fall short of the reactions found in "parasyphilis." In this respect our results differ from those of Plaut and Nonne. So far as concerns the mere occurrence of the reaction, we agree that in the spinal cases this is constant. We, however, find it to be constant with small quantities of cerebrospinal fluid, while the Hauptmann method obtains this result with large quantities only. We may point out that Stühmer's [54] results are more comparable with ours since, although he obtained a high percentage of positive results with the "Auswertungs-methode," many of his cases were already positive with the smaller quantities of fluid. It is clear that in Nonne's [39] view the strength of the reaction in cerebrospinal syphilis is slight. He states: "If the reaction is positive by the original method (0·2 c.c. of cerebrospinal fluid)," that is if the reaction is strong, "it is highly probable that the case is one of paralysis or tabo-paralysis, much less likely that it is cerebrospinal syphilis or pure tabes."

According to our results this view appears to be untenable. It will be seen that the reaction in the fluid of the spinal cases is at least as constant and as strong as in dementia paralytica, and we therefore dispute the suggestion that either the occurrence of the reaction in the cerebrospinal fluid or its strength has an obvious bearing upon the differential diagnosis between dementia paralytica and cerebrospinal syphilis. If, however, dementia paralytica is capable of being confused with purely cerebral syphilis, then the constant reaction in the former case and the negative in the latter will be of great diagnostic importance.

The differences in the results obtained by Hauptmann's method and our own are presumably due to differences in technique, the most important being in all probability the difference in antigens.

It appears to be quite certain that the advantage of the heart-cholesterin-antigen is particularly apparent in the "cerebral" cases.

It may be argued that the use of this antigen is objectionable since it levels up the diagnostic differences between general paralysis and cerebrospinal syphilis, but to retain these differences by the use of an inferior antigen would be an artificial proceeding and would tend to maintain a fundamental distinction between dementia paralytica and cerebrospinal syphilis which in our opinion does not exist.

(4) *Control Cases.*

In order to ensure the accuracy of the deductions drawn from the preceding cases, we have tested a number of sera and cerebrospinal fluids from patients in whom there was no syphilitic disease of the central nervous system. These controls are divisible into two groups :—

(*a*) Patients with syphilis, but without organic syphilitic disease of the central nervous system. This group will include syphilitic patients with non-syphilitic diseases of the central nervous system.

(*b*) Non-syphilitic patients with disease of the central nervous system.

(*a*) *Syphilitic patients without syphilis of the central nervous system :—*

No. of case	Result of first examination	No. of case	Result of first examination
9	serum 4.4.4.4.4. c.s.f. 0.0.0.0.0.	139	serum 4.4.4.3.2. c.s.f. 0.0.0.0.0.
29	4.4.4.4.4. 0.0.0.0.0.	154	4.4.4.4.4. 0.0.0.0.0.
35	4.4.4.4.4. 0.0.0.0.0.	155	4.4.4.3.1. 0.0.0.0.0.
38	4.4.4.4.4. 0.0.0.0.0.	166	4.4.4.4.4. 0.0.0.0.0.
63	4.4.4.4.4. 0.0.0.0.0.	171	4.4.4.4.4. 0.0.0.0.0.
68	4.4.4.4.2. 0.0.0.0.0.	178	4.4.4.4.0. 0.0.0.0.0.
78	4.4.4.4.4. 0.0.0.0.0.	187	4.4.4.4.4. 0.0.0.0.0.
79	4.4.4.4.4. 0.0.0.0.0.	196	4. - - - - 0.0.0.0.0.
88	4.2.0.0.0. 0.0.0.0.0.	206	4. - - - - 0.0.0.0.0.
105	4.4.4.4.4. 0.0.0.0.0.	208	2.0.0.0.0. 0.0.0.0.0.
129	4.4.4.2.0. 0.0.0.0.0.	209	0.0.0.0.0. 0.0.0.0.0.
138	4.4.2.1.0 0.0.0.0.0.		

These twenty-three cases include :—

Acute secondary syphilis	6	[Nos. 29 ; 38 ; 68 ; 78 ; 105 ; 154.]
Late secondary syphilis	2	[Nos. 129 ; 139.]
Symptomless syphilis	7	[Nos. 63 ; 88 ; 138 ; 166 ; 178 ; 196 ; 206.]
Tertiary syphilis	4	[Nos. 35 ; 79 ; 155 ; 171.]
Active congenital syphilis	2	[Nos. 9 ; 187.]
Inactive congenital syphilis	2	[Nos. 208 ; 209.]

Except in the case of the two inactive cases of congenital syphilis, the serum was invariably positive and the cerebrospinal fluid negative.

The two negative cases (Nos. 208 and 209) were instances of old congenital syphilis, in which the disease had almost died out. Such cases commonly give a negative reaction. (C.f. J. L. Gordon [15] on the effect of age upon the reaction in congenital syphilis.)

The cases of syphilis without involvement of the nervous system recorded in the literature reacted in a manner similar to ours. Plaut [40] in twenty-seven cases of manifest and latent syphilis found negative reactions in the cerebrospinal fluid in every case, while Boas and Lind [6] obtained the same result in ten. Hauptmann [16] also found no positive reactions in thirteen cases.

The most extensive observations on this subject have, however, been carried out by Altmann and Dreyfus [1], and it appears therefrom that in secondary syphilis, not apparently in the acute stage but after the healing of the chancre, a positive reaction may be found in the cerebrospinal fluid.

	Number of cases	Positive	Negative
Primary syphilis	7	0	7
Primary and secondary syphilis	21	0	21
Secondary syphilis	35	11	24
Tertiary syphilis	2	0	2

Several of these positive reactions were obtained only with high concentrations of cerebrospinal fluid, but, on the other hand, one was positive even with the smallest quantity by the original method.

Similar results have been described by Max Fraenkel [14], who found five cases of secondary syphilis positive in fifteen. These investigations lead us to believe that if we had tested a larger number of cases of late secondary syphilis, positive results might have been encountered. At the same time it is possible that when such cases give a positive result, a very careful clinical examination may reveal actual evidence of an organic lesion in the nervous system. If positive

reactions are found in cases in which there is no apparent lesion of the central nervous system, it might be thought that the test loses some of its practical value, since it has been universally held that a positive reaction in the cerebrospinal fluid indicates a syphilitic lesion of the central nervous system. The cases, however, are not really exceptions to the rule, since the positive results are clearly an index of an inflammatory process occurring in the meninges, a view which is also supported by the occurrence of a pleocytosis in the cerebrospinal fluid. From the investigations of Ravaut [47], and among many others of Altmann and Dreyfus, it is seen that a large number of cases of secondary syphilis show marked pathological changes in the cerebrospinal fluid (tension, pleocytosis, increased proteid content); and it is not therefore difficult to assume that a meningitic process is common, and that this in isolated cases may even lead to an exudation of Wassermann substances into the cerebrospinal fluid. Of great theoretical interest also is the case of Zaloziecki [60]. He obtained a positive reaction in a case of tuberculous meningitis occurring in a congenital syphilitic patient, which suggests that the inflammatory exudate derived from the meninges carried with it certain constituents of the blood serum including the Wassermann body, which thus was detectable in the cerebrospinal fluid. The case supports the view that a lesion of the pia mater is necessary for a passage of the reacting body into the fluid.

(*b*) *Non-syphilitic patients with disease of the central nervous system.*—The necessity for these controls lies in the fact that isolated instances of positive reactions in the cerebrospinal fluid have been reported in non-syphilitic conditions, the positive result being alleged to be due to the destruction of nervous tissue and the liberation of lipoids as occurs rarely in the serum as a result of a general anæsthetic. The cases quoted do not in our opinion require extended notice, since the reports of the best technicians have not confirmed them. Hauptmann [16] tested seventy-five cases of non-syphilitic disease of the nervous system, and although some of the patients were syphilitic, no positive reactions were observed.

We have examined examples of the following conditions:—

Old anterior poliomyelitis, Nos. 2, 172.

Neurasthenia, Nos. 4, 41, 174.

Spinal tumour, Nos. 31, 151.

Disseminated sclerosis, Nos. 34, 99, 103, 162, 168.

Cerebral tumour, Nos. 6, 40, 101, 113, 118, 121, 124, 179, 181.

Vascular conditions, Nos. 42, 49, 57, 81, 100, 163, 185, 190.

Syringomyelia, No. 43.
Peripheral neuritis, Nos. 136, 141, 180.
Epilepsy, Nos. 137, 195.
Amyotrophic lateral sclerosis, No. 153.
Subacute combined degeneration of cord, No. 173.
Primary optic atrophy. Pituitary tumour. No. 176.
Congenital ophthalmoplegia interna, No. 191.
Amentia, No. 193.
Acute delusional states, Nos. 194 and 195.

These forty-two cases gave negative reactions both in the serum and in the cerebrospinal fluid. It should be pointed out, however, that the reaction of No. 100 (vascular condition) showed slight inhibition in the cerebrospinal fluid, thus $\frac{\text{serum } 0.0.0.0.0.}{\text{cs.f. } 2.0.0.0.0.}$ This was a case of very slight transient hemiplegia, and although there was no evidence of syphilis obtainable, nevertheless a trivial thrombosis is precisely the form of lesion which might give a negative reaction in the serum and a slight positive in the cerebrospinal fluid. We have retained the case in its present position because 2.0.0.0.0. represents a negative reaction, and there was no other evidence of syphilis. Similarly No. 151 (spinal tumour) gave a reaction $\frac{0.0.0.0.0.}{1.0.0.0.0.}$ but in this case the significance, if any, is not clear.

Summary of the Incidence of the Reaction in Neurological Work.

In *dementia paralytica and tabo-paresis* a strong reaction is practically constant in both serum and cerebrospinal fluid. A negative reaction will make a diagnosis of these conditions highly improbable.

In *tabes dorsalis* the reaction is positive in serum and cerebrospinal fluid, except when the condition has subsided as a result of time or treatment. The strength of the reaction is often not so great as in dementia paralytica; on the other hand, it is often as great.

In untreated *cerebrospinal syphilis* the reaction in the cerebrospinal fluid varies according to the site of the lesion. When the spinal cord is involved it is positive and usually very strong, but when the spinal cord is not involved it is very inconstant and when present weak. The reaction is present most often in recent lesions. In treated cases the reaction is present in the cerebrospinal fluid according to the efficiency or otherwise of the treatment.

In *syphilis* without an organic syphilitic lesion of the central nervous system, the reaction in the cerebrospinal fluid is negative. The occurrence of a reaction in the cerebrospinal fluid, therefore, indicates a syphilitic lesion of the central nervous system.

In *non-syphilitic diseases* of the central nervous system the reaction is negative.

CHAPTER III.—THE EFFECT OF ANTI-SYPHILITIC TREATMENT UPON THE WASSERMANN REACTION.

Introduction.

As first pointed out by Citron the incidence of the Wassermann reaction is dependent largely upon whether anti-syphilitic treatment has or has not been applied; he found that more numerous positive reactions were obtained in those cases of syphilis which had not been treated, than in those which had been treated with mercury. At first, however, the effect of mercury upon the reaction was not generally recognized, chiefly because this substance was seldom successful in turning a positive test into a negative; and it was only on the publication of the quantitative technique of Thomsen and Boas, that it became obvious that a diminution in the strength of the reaction was a constant feature of treatment, even though the fully negative result was not often obtained.

Following the introduction of salvarsan it was found that the reaction could be rapidly influenced in certain cases and, owing to the shorter period of observation necessary, it was possible to estimate with a certain degree of accuracy when the reaction might be expected to become negative. We early found that the effect of intra-muscular injections of salvarsan upon the reaction differed greatly according to the stage of the disease present. Thus according to our results [26], the reaction in primary syphilis usually became negative in five weeks. No case failed to become negative. In secondary syphilis the average was eight weeks and one third of the cases failed to become negative. In early latent syphilis negative reactions were obtained in ten weeks, while in tertiary syphilis only one negative reaction was observed.

From these figures it was clear that the longer the infection had been present, the more difficult was it to obtain a negative reaction.

Later, when intravenous injections were used and a larger total dose, the effect was found to be more definite. The time required to produce a negative reaction in secondary syphilis was slightly reduced,

and no case failed to become negative, while in tertiary cases the negative results were more frequent.

With improvements in the technique of the reaction, and particularly with the introduction of the heart-cholesterin antigen, we found that the effect of anti-syphilitic treatment became less obvious in that it required a considerably longer period of time to render certain cases negative. Since the test was very much more searching, it was possible to detect the reacting body in the serum for a longer time than with the older methods. It is therefore necessary to give new average figures according to the technique at present in use.

In discussing the effect of anti-syphilitic treatment we are compelled to confine ourselves to the effect of salvarsan and neo-salvarsan, since we know of no recent records relating to the action of mercury. The exact effect of this latter drug has never been satisfactorily worked out, since research into the question ceased after the introduction of the more potent substances.

The Effect of Treatment upon the Reaction in Acute Syphilis.

Examples of the Effect of Treatment in Acute Secondary Syphilis.

Case M. L.—Treatment, 2·7 grm. neo-salvarsan in five days.

	Serum
At time of first dose	4.4.4.4.4.
2 *weeks* after first dose	4.4.4.4.4.
4 —— —— —— —— ——	4.4.4.4.0.
6 —— —— —— —— ——	4.2.0.0.0.
8 —— —— —— —— ——	0.0.0.0.0.

Case J. M.—Treatment, 2·0 grm. neo-salvarsan in seven days.

	Serum
At time of first dose	4.4.4.4.4.
2 *weeks* after first dose	4.4.4.4.4.
4 —— —— —— —— ——	4.4.4.4.3.
6 —— —— —— —— ——	4.4.4.1.0.
8 —— —— —— —— ——	4.4.4.2.0.
10 —— —— —— —— ——	4.4.0.0.0.
12 —— —— —— —— ——	0.0.0.0.0.

Case A. T.—Treatment, 2·4 grm. neo-salvarsan in five days.

	Serum
At time of first dose	4.4.4.4.4.
2 *weeks* after first dose	4.4.4.4.4.
4 —— —— —— —— ——	4.4.4.4.4.
6 —— —— —— —— ——	4.4.4.4.0.
8 —— —— —— —— ——	4.2.0.0.0.
10 —— —— —— —— ——	0.0.0.0.0.

We have examined nine cases of acute secondary syphilis at regular short intervals in order to arrive at the shortest time occupied in reducing the positive reaction to negative. The method of treatment was to inject intravenously three doses of neo-salvarsan, within a period of five to ten days. The total dosage varied from 2·0 to 2·7 grm. It was found that the shortest interval before the establishment of a negative reaction was one and a half months and the longest three months. The average of the nine cases was two and a half months. Comparing these results with those formerly obtained by us when using salvarsan and the old Wassermann technique, it is seen that the reaction tends to persist for a slightly longer period with the newer method.

The Effect of Treatment upon the Reaction in Tertiary Syphilis.

In treating cases of tertiary syphilis we soon found that the effect of salvarsan, as measured by the Wassermann reaction, was entirely different compared with the effect in secondary syphilis. Instead of achieving the desired result regularly in a few weeks, we were in many cases unable to detect any diminution in the reaction over a period of many months with the old methods. Sometimes when the reaction was feeble at the outset a negative test with heart-antigen was eventually attained, but in the majority of these the sera were found to give a positive reaction again with the heart-cholesterin antigen. With the methods at present in use we are forced to confess that the production of a negative reaction in tertiary syphilis is a relatively rare phenomenon. Without doubt, however, this result, at any rate in hospital practice, is in part due to the difficulties in dealing with the patients. In almost every case the symptoms rapidly disappear after the first dose, and it is therefore difficult to induce the patients to re-enter the hospital for a chronic intermittent form of treatment. By this method it is, of course, possible to demonstrate a more marked effect of treatment, but even then it is still a question of many months before this is apparent as opposed to a few weeks in the acute stages.

The effect of treatment in the period between the acute secondary and tertiary symptoms depends upon the age of the infection; the earlier cases correspond more to the acute type, while the later tend more towards the tertiary. When the acute stage is passed, however, the reaction soon becomes much more refractory to treatment.

The following cases are examples of the effect of treatment as measured by the present technique.

Examples of the Effect of Treatment in Tertiary Syphilis.

Case A. S.—Treatment, 1·4 grm. neo-salvarsan at first, 0·9 grm. neo-salvarsan at third month.

	Serum
At time of first dose	4.4.4.1.0.
2 *months* after first dose	4.4.1.0.0.
4 ——	4.4.1.0.0.
6 ——	4.3.1.0.0.
8 ——	- - - - -
10 ——	3.2.0.0.0.

Case E. M.—Treatment, 4·2 grm. neo-salvarsan in six months.

	Serum
At time of first dose	4.4.4.4.4.
2 *months* after first dose	4.4.4.4.4.
4 ——	4.4.4.4.4.
6 ——	4.4.4.4.4.
8 ——	4.4.4.4.4.
10 ——	- - - - -
12 ——	4.4.4.3.0.

Case H. G.—Treatment, 1·7 grm. salvarsan in six days.

	Serum
At time of first dose	4.4.4.4.3.
2 *months* after first dose	4.4.4.3.0.
4	4.4.4.0.0.
6 ——	4.4.4.0.0.
8	4.4.4.0.0.
19 ——	4.4.4.4.0.
26 ——	4.4.4.4.0.

The comparatively small effect of anti-syphilitic treatment upon the Wassermann reaction in chronic syphilis might be due to two causes. Firstly, the spirochætes may be readily destroyed and still the reaction may be produced, or, secondly, the spirochætes may not be readily destroyed and thus the reaction may continue. Since it is generally admitted that the phenomenon directly depends upon the presence of the spirochæte, the first assumption may be looked upon as improbable, and particularly when it is remembered that under certain circumstances the spirochætes admittedly avoid destruction. We refer to the relatively frequent occurrence of relapses in the nervous system after an apparently complete cure, showing that spirochætes occupying this position commonly escape a destructive agent in the blood-stream. Again we may refer to the extraordinary frequency of syphilitic affections of the aorta and large vessels. In a series of cadavers taken at random, Turnbull and one of us [P. F.] found that in the great majority of cases in which a positive Wassermann reaction was found,

syphilitic mesaortitis was present, often unaccompanied by any other syphilitic lesion. This result suggests that spirochætes lodged in the walls of the large arteries are largely immune to the effect of a spirochæticidal substance in the blood-stream, and this view is supported by the fact that the Wassermann reaction is usually more resistant to treatment in mesaortitis than in any other manifestation of syphilis. So commonly is mesaortitis found in the *post-mortem* room and so resistant are these cases to treatment, that it may almost be said that a chronic case of syphilis, in which the reaction is readily reduced, is unlikely to show mesaortitis, and conversely if no effect can be produced upon the reaction by treatment, the probability of the presence of mesaortitis will be increased.

From these considerations it appears probable that in the chronic cases of syphilis, spirochætes may commonly occupy positions which do not readily come under the influence of treatment. It will then happen that when a case of cutaneous ulceration has been treated, the few spirochætes are destroyed and the lesion healed, but very little effect is observed upon the Wassermann reaction, because another focus in the aorta or central nervous system continues undisturbed the production of the reacting bodies.

The Effect of Treatment upon the Reaction in Syphilis of the Central Nervous System.

Variations in the strength of the Wassermann reaction following anti-syphilitic treatment in diseases of the nervous system do not appear to have been noticed to any great extent.

Plaut (1909) [41] was unable to detect any definite diminution in the reaction in the serum or cerebrospinal fluid in cases of dementia paralytica or even in cerebral syphilis, although in both conditions a great fall in the cell content of the cerebrospinal fluid might occur.

In 1913 Plaut, Rehm and Schottmüller [45] pay very little attention to the question. They state that previously to the introduction of salvarsan, no effect was produced in dementia paralytica by anti-syphilitic treatment; with salvarsan, however, a distinct diminution in the reaction in the cerebrospinal fluid may occur; indeed in rare cases this may become negative.

In general it may be said that anti-syphilitic treatment is not expected to exert any definite beneficial effect upon the reaction in dementia paralytica, while in tabes dorsalis a diminution may be more

frequently met with. As regards the behaviour of the reaction in the cerebrospinal forms, it cannot be said that any definite opinion has been expressed.

The failure of the reaction in the cerebrospinal fluid in dementia paralytica to respond to treatment is largely assumed from the work of Plaut in 1909. At the same time it must be pointed out that the intervals between the tests in Plaut's cases were short and were hardly sufficient to allow of the detection of any alteration if it had occurred. Again, it is so little the practice to apply intensive treatment to "general paralytics" that the number of observations is meagre. Further, if such treatment is applied to early cases, it is very difficult to keep them under observation, while in the later asylum cases, little beneficial result can be expected. Thus, on the evidence available, it appears premature to assume that the reaction cannot be diminished in the cerebrospinal fluid of cases of dementia paralytica.

In tabes dorsalis the general opinion upon the effect of treatment is probably deduced from the variable occurrence of the reaction. For instance, if it is relatively common to find stationary cases with negative Wassermann reactions it is not difficult to suppose that these have been produced, at least in part, by treatment. We are, however, unacquainted with any direct demonstration of the effect of anti-syphilitic remedies in tabes dorsalis.

This question would appear to be one of considerable importance, since it must be held that variations in the strength of the reaction in the cerebrospinal fluid are in most cases indications of fluctuations in the intensity of the syphilitic process in the central nervous system. Thus the effect of treatment upon the reaction in the cerebrospinal fluid assumes an important prognostic rôle.

In classifying the results of our investigations we have met with considerable difficulty. As will appear from the works of Dr. Head and Dr. Fearnsides, some cases of "general paralysis" and "tabes dorsalis" when submitted to intensive treatment have behaved in such a manner as to render their inclusion among the group of "parasyphilitics" anomalous. Although by definition and supposed pathology these cases should be incurable, nevertheless the salvarsan injections have in many instances produced a profound amelioration. This fact and certain other considerations have led Dr. Head and Dr. Fearnsides to transfer several cases which might at first sight have been called "general paralysis" and "tabes" to the group of "cerebrospinal syphilis." The diseases dementia paralytica and tabes dorsalis are clinical concepts,

and, as we have already pointed out [29], every example does not necessarily fall into the same pathological group. They are not all "parasyphilitic" in the original sense, but some are actively syphilitic, and therefore to group these cases together would produce a clinical rather than a pathological classification.

In the following account of the result of treatment upon the Wassermann reaction we have adopted the clinical classification in order to make our results comparable with those of previous workers; nevertheless it must be clearly stated that from our pathological point of view such a method is incorrect, and, also, in particular cases may even be unacceptable from the refined clinical standpoint.

Dementia Paralytica and Tabo-paresis.

The effect of treatment upon the Wassermann reaction in dementia paralytica is very difficult to gauge in hospital practice owing to the lack of control over the patients; nevertheless, in the few cases examined we have often found a very material diminution which has corresponded with an improvement in the clinical condition.

When the effect of treatment is to be estimated in disease of the central nervous system, the cerebrospinal fluid only has any direct bearing, since the serum is also under the influence of any other syphilitic focus in the body and may remain unaltered in strength, although the focus in the nervous system, as shown by a negative reaction in the cerebrospinal fluid, has resolved. Thus in order to follow treatment it is essential to perform lumbar puncture periodically, a proceeding which is sometimes resented.

Examples:

Case 32.— Dementia paralytica.

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.4.4.2.1.	4.4.4.3.2.	0·6 grm. salvarsan.
1 *month* after first dose	——	——	0·6 grm. salvarsan.
2 *months*	——	——	
3	——	——	
4	——	——	
5	——	——	
6	——	——	
7	——	——	
8	——	——	
9	——	——	
10	——	——	
11	——	——	
12	——	——	
13	——	——	
14	4.4.4.4.0.	4.4.4.2.0.	

Case 20.—[Tabo-paresis].

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.4.4.3.1.	4.4.4.4.1.	1·8 grm. neo-salvarsan
1 *month* after first dose	——	——	
2 *months*	——	——	
3	——	——	
4	4.4.4.1.0.	——	0·9 grm. neo-salvarsan.
5	——	——	
6	——	——	
7	——	——	
8	——	——	
9	——	——	
10	——	——	
11	4.4.4.3.2.	4.4.4.2.0.	

Case 90.—[Tabo-paresis].

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.4.4.4.2.	4.4.4.4.0.	2·7 grm. neo-salvarsan.
1 *month* after first dose	——	——	
2 *months*	——	——	
3	——	——	
4	——	——	
5	——	——	
6	4.4.4.4.4.	4.4.3.0.0.	

Case 120.—[Probably encephalitis simulating dementia paralytica].

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.2.0.0.0.	4.3.2.0.0.	0·6 grm. salvarsan.
1 *month* after first dose	——	——	
2 *months*	——	——	
3	——	——	
4	——	——	
5	——	——	
6	——	——	
7	——	——	
8	0.0.0.0.0.	0.0.0.0.0.	0·9 grm. neo-salvarsan.
9	——	——	
10	——	——	
11	0.0.0.0.0.	——	

On examination of the four cases illustrated, it will be seen that three (Nos. 20, 90, and 120) showed a definite diminution in the reaction in the cerebrospinal fluid, while the fourth (No. 32) was unaltered. It should be mentioned that Nos. 90 and 120 are no longer looked upon as uncomplicated cases of "parasyphilis," but are now included among the active syphilitic processes.

It would appear from these results that salvarsan treatment is not without effect upon "general paralysis" and "tabo-paralysis" in the ordinary usage of these terms. In some cases, perhaps, the result of treatment may be neglected, but in others it is so marked as to suggest that the pathological process is not identical in all. When the effect of treatment is most pronounced, it is often found that there is evidence

of an active involvement of the meninges, that is to say, such cases appear to be transitional forms between the true dementia paralytica and cerebrospinal syphilis in the sense of our previous publication [29]. In pure "parasyphilis" we assume a lesion practically confined to the nerve structures and resistant to treatment. In most cases of "parasyphilis," however, the lesion is not so restricted, and actively involves the vascular structures. This element of "parasyphilis" will be curable.

Tabes Dorsalis.

Since the Wassermann reaction in tabes dorsalis may be found to be negative, it might be expected that treatment in these cases would have a greater effect than in dementia paralytica. We have, however, been unable to demonstrate any marked difference, as the following examples will show. When the anti-syphilitic treatment consists only of mercury, it is true that after a prolonged period a diminution may be found in tabes dorsalis, while none is evident in dementia paralytica. This result, however, is largely due to the early death of the "paralytic" before mercury has had time to reduce the disease to a state of chronicity as in tabes dorsalis.

Examples:

Case 37.—

	Serum	Cerebrospinal fluid	Treatment
At time of first dose ..	4.4.2.0.0.	.. 4.4.3.1.0.	.. 0·9 grm. neo-salvarsan.
1 *month* after first dose	———	.. ———	.. 0·9 grm. neo-salvarsan.
2 *months*	4.3.2.0.0.	.. ———	
3	———	.. ———	
4	———	.. ———	
5	4.4.4.2.0.	.. ———	
6	———	.. ———	
7	4.4.4.2.0.	.. 4.4.2.0.0.	.. 0·9 grm. neo-salvarsan.
8	———	.. ———	
9	———	.. ———	
10	———	.. ———	
11	4.4.4.2.0.	.. 4.4.2.0.0.	

Case 150.—

	Serum	Cerebrospinal fluid	Treatment
At time of first dose ..	4.4.4.4.2.	.. 4.4.3.0.0.	.. 2·7 grm. neo-salvarsan.
1 *month* after first dose	———	.. ———	
2 *months*	———	.. ———	
3	———	.. ———	
4	———	.. ———	
5	———	.. ———	
6	———	.. ———	
7	———	.. ———	
8	———	.. ———	
9	———	.. ———	
10	———	.. ———	
11	4.4.4.4.4.	.. 4.4.1.0.0.	

Case 125.—

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.4.4.4.3.	4.4.4.4.3.	2·7 grm. neo-salvarsan.
1 *month* after first dose	———	———	
2 *months* ———	4.4.4.4.1.	———	
3 ———	4.4.4.4.4.	4.4.4.0.0.	0·3 grm. neo-salvarsan.
4 ———	4.4.4.4.2.	———	2·2 grm. neo-salvarsan.
5 ———	4.4.4.4.1.	———	
6 ———	4.4.4.4.2.	———	
7 ———	———	———	
8 ———	4.4.4.4.0.	4.4.2.0.0.	

Cases Nos. 37 and 150 were both classical examples of tabes dorsalis, and the treatment administered resulted in no obvious alteration in the reaction. In No. 125, however, a very material improvement resulted, and this coincided with a clinical improvement. This case has been transferred to the cerebrospinal syphilis group owing to evidence of an active meningeal lesion, and probably represents a transitional form between the pure uncomplicated "tabes" and those "active" lesions which do not primarily involve the nerve-tissues proper.

We conclude, therefore, from these results that anti-syphilitic treatment is almost without effect upon the pure "parasyphilitic" tabes dorsalis, as also upon the pure dementia paralytica; but in a number of cases diagnosable as "tabes," or "general paralysis," treatment has a very definite effect, and such cases show clinical evidence of an associated interstitial syphilis.

It should be noticed that although treatment has little or no effect upon the reaction in the pure "parasyphilitic" cases, this result cannot be looked upon as in any way characteristic of this condition. We have already shown that in many cases of pure tertiary syphilis, treatment is apparently abortive; thus it cannot strictly be said that "parasyphilis" is any more incurable than tertiary syphilis. If the index of "cure" is taken to be the disappearance of clinical symptoms, the difference between the course of "parasyphilis" and tertiary syphilis is marked; but, judging the Wassermann reaction to be a measure of the effect upon the virus, it is seen that the apparent effect of treatment in tertiary syphilis is largely illusive. At any rate, the difference is purely one of degree, and it is too slight to support the view that "parasyphilis" is a condition distinct from syphilis.

Cerebrospinal Syphilis.

Turning to those cases in which the syphilitic process is usually described as being "active" as opposed to "parasyphilitic," we find

that the effect of treatment is very much more marked; indeed, in most cases the reaction in the cerebrospinal fluid may readily be reduced to negative.

Example of acute cerebrospinal syphilis:

Case 59.—

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.4.4.4.4.	4.4.4.4.3.	1·8 grm. neo-salvarsan.
1 *month* after first dose	4.4.4.4.4.	4.4.4.1.0.	0·9 grm. ,,
2 *months*	4.4.4.4.3.	4.4.3.0.0.	0·9 grm. ,,
3			
4			
5	4.4.1.0.0.	0.0.0.0.0.	0·9 grm. ,,
6	1.0.0.0.0.		0·9 grm. ,,
7			
8			
9			
10			
11			
12	2.0.3.0.0.		

In this case of acute cerebrospinal syphilis the onset of the condition was seven months after infection, the patient being in the secondary stage. He had undergone six months' mercurial treatment. It will be seen that the salvarsan injections had a rapid effect upon the cerebrospinal fluid, which was found to be negative after five months. The serum was also quickly reduced to normal, although the effect was not so prompt as in the cerebrospinal fluid.

Examples of chronic cerebrospinal syphilis:

Case 19.—

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.4.4.4.3.	4.4.4.3.2.	1·5 grm. neo-salvarsan.
1 *month* after first dose			
2 *months*			
3			
4			
5			
6			
7			
8	4.4.4.4.3.		
9	4.4.4.4.3.	0.0.0.0.0.	0·9 grm. neo-salvarsan.

Case 74.—

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.4.4.4.2.	4.4.4.3.1.	2·7 grm. neo-salvarsan.
1 *month* after first dose			
2 *months*			
3			
4	4.4.4.3.0.		
5			
6			
7			
8	4.4.4.3.0.	0.0.0.0.0.	

Case 134.—

	Serum	Cerebrospinal fluid	Treatment
At time of first dose	4.4.4.4.0.	4.4.4.4.4.	0·6 grm. salvarsan.
1 *month* after first dose	———	———	0·9 grm. neo-salvarsan.
2 *months*	4.4.4.4.4.	— ———	
3	———	———	
4	4.2.1.0.0.	4.2.0.0.0.	0·9 grm. neo-salvarsan.

Case 146.—

	Serum	Cerebrospinal fluid	Treatment
3 *months* before first dose	4.4.4.4.4.	4.4.4.4.2.	
2 *months*	— ———	———	
1 *month*	———	———	
At time of first dose	———	———	1·8 grm. neo-salvarsan.
1 *month* after first dose	———	— ———	
2 *months*	———	———	
3	———	———	
4	4.4.3.2.0.	4.1.0.0.0.	0·9 grm. neo-salvarsan.

From the few examples detailed above it is clear that the positive reaction in the cerebrospinal fluid of cases of acute and chronic syphilis of the central nervous system is rapidly influenced by specific treatment, although the serum in the latter condition is less affected, as in chronic syphilis elsewhere. When it is remembered that the reaction in the cerebrospinal fluid of pure "parasyphilis" is little affected by treatment, while in cerebrospinal syphilis the effect is pronounced, it would appear that the result of treatment may be taken as some *indication of the presence or absence of "parasyphilis."* If, after sufficient treatment the reaction in the cerebrospinal fluid rapidly diminishes, the probability is greatly in favour of a lesion mostly lymph-vascular, and thus the prognosis is much better than when the reaction is found to be resistant to treatment. In the latter case the presence of a "parasyphilitic" nerve lesion is to be suspected and the prognosis should be guarded.

The reason for the relative futility of treatment in the "parasyphilitic" conditions is doubtful. According to some, the source of the reacting substance in "parasyphilis" is the degenerating nerve-cell, and since this degeneration is progressive, the supply of reacting substance will be continuous and unaffected by treatment. This explanation is, however, highly improbable. The origin of the reacting substance everywhere is the specific activity of the *Spirochæta pallida* exerted upon the neighbouring cells. When the nerve-cells are intoxicated by this organism, they no doubt give rise to a quantity of reacting substance, but the subsequent degeneration has in it no syphilitic element and no specific bodies will be liberated.

We consider that the more probable explanation for the lack of

effect in "parasyphilis" and the marked effect in syphilis, is that the focus of origin of the reacting substance in the former case is not resolved by treatment, while in the latter it rapidly disappears. Cerebrospinal syphilis is a lesion chiefly or entirely confined to the lymph-vascular tissues of the brain and practically always involves the meninges. The products of this inflammation including the Wassermann substance appear in the cerebrospinal fluid as an exudate from the surrounding meninges, and thus if the inflammatory process is resolved by treatment the local production of Wassermann substances will rapidly cease. If comparison may be made with active syphilitic lesions elsewhere, it is probable that a gummatous meningitis may be entirely healed in a few days, and thus the arrest of reacting bodies will be sudden; nevertheless in practice it is always found that the reaction persists for several months and gradually diminishes in strength, and, in our view, this is due merely to the stagnation of the cerebrospinal fluid.

If, therefore, the behaviour of the cerebrospinal fluid after treatment of cerebrospinal syphilis is readily explicable, the same cannot be said of "parasyphilis." In this condition the syphilitic process persists and therefore it is clear that the *Spirochæta pallida* must persist in spite of treatment. This phenomenon might be due to the development of a resistant strain of spirochætes, when treatment throughout has been by the same drug, but it would not explain the futility of salvarsan, when a patient had previously been treated by mercury. It may also be said that the assumption of a resistant strain of spirochætes is not supported by much experimental evidence.

A more probable explanation of the failure of treatment to destroy the spirochæte is to be found in the case described by us in 1911 [27]. An infant which died after salvarsan treatment was found to have arsenic in all the organs examined with the exception of the brain, and from this it may be deduced that arsenic does not penetrate to the substance of the brain. Such an occurrence would of course account for the survival of spirochætes situated in the brain-tissue proper, as in "parasyphilis," and for the continuation of the supply of Wassermann substances. Since, however, the passage of these substances into the cerebrospinal fluid depends upon a pathological alteration of the pia mater, it might be objected that the alteration present in "parasyphilis" should be resolved and the exudation of Wassermann bodies prevented. On the other hand, the affection of the meninges in pure "parasyphilis" is not a primary process due to the *Spirochæta pallida*

locally, but is secondary to the micro-organism lying in the nerve-tissues at a distance; thus the infiltration of the pia will persist so long as the spirochæte persists, in spite of the fact that the arsenic may have free access to the meninges.

The Effect of Treatment in Producing Exacerbations of the Reaction.

It has long been recognized that injections of salvarsan or mercurial inunctions sometimes produce an exacerbation of the Wassermann reaction, so that it may become positive when before treatment it was negative, or there may be a quantitative increase in a previously positive reaction. Since the introduction of salvarsan these exacerbations have become more common, and the word "provocative" has been applied to an injection which produces this result. The phenomenon has considerable theoretical interest, and also, to a certain extent, a practical value, especially in neurology.

The practical utility of a "provocative" injection lies in its intentional application in order to produce a positive reaction in a suspected case of syphilis, in which it was previously negative. Thus the "provocative" injection may have considerable diagnostic value.

Further, it has been laid down that if an individual with a negative reaction, but known to have had syphilis previously, does not show an exacerbation of the Wassermann reaction as a result of an injection of salvarsan, he may be looked upon as being cured.

In our opinion this latter assumption is without sufficient foundation; the only deduction to be made from such an occurrence is that at the time of the injection the individual had no active syphilitic lesion, but it does not preclude the possibility of an exacerbation or relapse of syphilis at a later date.

In order to disclose an exacerbation after a "provocative" injection, it is advisable to test the reaction more than once, since the time of its occurrence cannot be accurately foretold. Suitable periods are one and two weeks after the injection, but if only one test is to be made, this may be applied ten days after.

It is important that only one dose be given, since a repetition of the injection may abort an exacerbation before it has developed sufficiently to be detectable.

Examples of "provocative" reactions:

Case 144.—Stationary tabes dorsalis.

		Serum	Cerebro-spinal fluid
10.7.1912		0.0.0.0.0.	0.0.0.0.0.
16.7.1912		- - - - -	0.0.0.0.0.
18.7.1912	Injection 0·6 grm. neo salvarsan	0.0.0.0.0.	- - - - -
20.7.1912		0.0.0.0.0.	- - - - -
22.7.1912		0.0.0.0.0.	- - - - -
24.7.1912		- - - - -	0.0.0.0.0.
25.7.1912		1.1.0.0.0.	- - - - -
29.7.1912		- - - - -	0.0.0.0.0.
30.7.1912		4.4.4.1.0.	- - - - -
1.8.1912	Injection 0·9 grm. neo-salvarsan	- - - - -	- - - - -
7.8.1912		4.4.4.3.1.	1.0.0.0.0.
10.8.1912	Injection 0·9 grm. neo salvarsan	- - - - -	- - - - -
8.10.1912		0.0.0.0.0.	0.0.0.0.0.
14.10.1912	Injection 0·6 grm. neo-salvarsan	- - - - -	- - - - -
23.10.1912		0.0.0.0.0.	- - - - -

A "provocative" reaction appeared in the serum, but not in the cerebrospinal fluid seven to twelve days after the injection.

Case 94.—Cerebrospinal syphilis.

		Serum	Cerebrospinal fluid
16.10.12		0.0.0.0.0.	4.4.4.3.0.
21.10.12	Injection 0·9 grm. neo-salvarsan	- - - - -	- - - - -
30.10.12		0.0.0.0.0.	- - - - -
31.10.12	Injection 0·9 grm. neo-salvarsan	- - - - -	- - - - -
2.11.12		0.0.0.0.0.	- - - - -
5.11.12		0.0.0.0.0.	4.4.4.3.0.
17.1.13	Injection 0·9 grm. neo-salvarsan	- - - - -	- - - - -
22.1.13		4.3.2.0.0.	- - - - -
23.4.13		1.0.0.0.0.	0.0.0.0.0.

In this case no "provocation" of the reaction occurred within nine days of the first dose, although the patient was clearly syphilitic. The reaction in the serum subsequently became positive, but it is doubtful whether this was due to the injection given five days before.

Case 106.—Cerebrospinal syphilis.

		Serum	Cerebrospinal fluid
24.1.12		4.4.4.4.4.	4.4.0.0.0.
27.1.12	Injection 0·6 grm. salvarsan	- - - - -	- - - - -
31.1.12	Injection 0·6 grm. salvarsan	- - - - -	- - - - -
20.3.12		4.3.3.2.0.	- - - - -
9.7.12	Injection 0·6 grm. salvarsan	- - - - -	- - - - -
10.7.12		0.0.0.0.0.	0.0.0.0.0
17.7.12		4.3.0.0.0.	- - - - -

A "provocative" reaction occurred seven days after the injection.

Case 110—Hemiplegia.

		Serum	Cerebrospinal fluid
10.1.12		0.0.0.0.0.	0.0.0.0.0.
	Mercurial injections		
7.2.12		4.3.0.0.0.	- - - - -

An example of the "provocative" effect of mercury.

The value of the "provocative" injection for diagnostic purposes is probably greater in neurology than in general syphilitic work, because in this branch there are more conditions resulting from very trivial lesions which may fail to give a Wassermann reaction at first. Further, the central nervous system is a situation commonly occupied by the spirochæte while in a latent condition. Thus in neurology this test may have a certain value, but at the same time it must not be forgotten that it is often abortive.

The phenomenon is probably of a similar nature to the "Herxheimer reaction" or to "spirochæte fever," that is to say, it is probably due to the sudden destruction of a focus of spirochætes, and thus a sudden intoxication of the neighbouring cells by liberated "toxins." This would have the effect not only of producing a quantity of Wassermann substances locally, but it might also disturb the balance between virus and cell, so that the former might be enabled to pass into a greater state of activity.

Variations in the Reaction without Treatment.

We have already described the diminution or exacerbation of the Wassermann reaction which may occur after anti-syphilitic treatment; but it is also found that such variations occur without any treatment having been applied. The effect of an anti-syphilitic drug is to cure the symptoms of the disease by destroying the spirochæte, and thus the reaction becomes negative; but the spirochæte may be destroyed, and the symptoms healed by the natural protective processes without any active medical intervention, in exactly the same manner as may occur in other infective conditions.

This is the explanation of the spontaneous healing of the secondary symptoms and the gradual diminution of the Wassermann reaction which may occur in the entire absence of anti-syphilitic treatment. The common finding of a negative reaction in stationary tabes is also an example; the syphilitic process has died out spontaneously.

We have been able to record this phenomenon in cases in which treatment had been omitted on the grounds that the patients were "parasyphilitic."

Case 142.—Tabes dorsalis.

14.12.11	..	serum	4.4.4.1.0.	Cells in cs.f. = 21 per c.mm.
		cs.f.	4.4.4.0.0.	
7.5.13	..	serum	4.4.4.4.2.	Cells in cs.f. = 6 per c.mm.
		cs.f.	4.4.1.0.0.	

Case 86.—Dementia paralytica (later classed as cerebrospinal syphilis).

13.3.12	..	serum	4.4.3.3.0.	Cells in cs.f. = 63 per c.mm.
		cs.f.	4.4.4.4.0.	
16.4.13	..	serum	4.4.4.4.4.	Cells in cs.f. = 19 per c.mm.
		cs.f.	4.4.0.0.0.	

In these two cases the decrease in the reaction in the cerebrospinal fluid suggested a certain degree of improvement in the local nervous condition, and in one (No. 86) this view was supported by a marked amelioration in the clinical state. Variations in the reaction in the opposite direction, that is, spontaneous exacerbations, are, of course, common and indicate a relapse, and of this many examples might be quoted. If the blood-test is performed sufficiently often it will be found that the relapse of the Wassermann reaction nearly always precedes a clinical relapse by several weeks or months, and thus the occurrence of the latter may be prevented by suitable treatment.

A relapse occurring in the central nervous system, however, presents some details of interest; thus in the great majority of cases, its effect is apparent in the cerebrospinal fluid before the serum. This result might be expected since the reacting substances are poured directly into the cerebrospinal fluid as an exudate and are only detectable in the serum, when they have accumulated in sufficient quantity. It is for this reason that the cases exhibiting a "nerve relapse" often yield a negative reaction in the serum.

In the following case, No. 123, the patient was examined experimentally merely because of the occurrence of headaches within two years of infection. He was found to have a positive Wassermann reaction in the cerebrospinal fluid and a great increase in the cell-content, although the serum was negative and no physical signs of disease were manifest. In this case the lesion was detected by the reaction before the onset of signs and the serum became positive at a later date only. The attack aborted as the result of intensive treatment

as shown by the decreasing reaction in the cerebrospinal fluid and the reduction of the cell-content to normal.

Case 123.—Late Secondary Syphilis with Relapsed Meningo-encephalitis.

		Serum	Cerebrospinal fluid	
25-30.11.1911	Injection 1·2 grm. salvarsan	- - - - -	- - - - -	Superficial ulceration of tongue fourteen months after infection. Twelve months Hg.
3.4.1912		4. - - - -	- - - - -	
13.11.1912		1.0.0.0.0.	- - - - -	Headaches.
28.11.1912	Injection 0·9 grm. neo-salvarsan	0.0.0.0.0.	4.4.1.0.0. 85 cells per c. mm.	No nervous symptoms.
4.6.1913		4.4.4.4.2.	4.4.4.4.3. 90 cells per c.mm.	Headaches. Mental irritability. No physical signs.
6.6.1913	Injection 0·6 grm. neo-salvarsan			
12.6.1913	Injection 0·9 grm. neo-salvarsan			
18.6.1913	Injection 0·9 grm. neo-salvarsan			
23.6.1913	Injection 0·9 grm. neo-salvarsan			
26.7.1913	Injection 0·9 grm. neo-salvarsan			
31.7.1913		4.4.4.3.0.	- - - - -	
13.8.1913		4.3.2.0.0.	4.4.4.0.0. 3 cells per c.mm.	
19.9.1913		4.4.3.0.0.	- - - - -	
19.11.1913		0.0.0.0.0.	- - - - -	

It will be noticed that the patient escaped observation for six months after a single dose of neo-salvarsan. This dose probably alleviated the headaches but did not materially hinder the development of the disease. On his return he was found to be in a condition worse than before. This is the phenomenon often described as a "nerve relapse," and is sometimes erroneously ascribed to the salvarsan injection, instead of to the progress of the disease after insufficient treatment.

The following case also illustrates the exacerbation of the reaction in the serum; the cerebrospinal fluid was not tested, and therefore it is not known whether this became positive before the symptoms appeared. The exacerbation was transient and subsided without treatment.

Case 91.—Cerebrospinal syphilis.

		Serum	Cerebrospinal fluid	
10.7.1912	Injection 0·6 grm. salvarsan	4.4.3.0.0.	4.4.4.0.0.	
17.7.1912	Injection 0·6 grm. salvarsan	- - - - -	- - - - -	
15.1.1913	Injection 0·9 grm. neo-salvarsan	3.2.1.0.0.	1.0.0.0.0.	
22.1.1913	———	3.2.1 0.0.	- - - - -	
18.6.1913	———	3.0.0.0.0.	- - - - -	Onset of herpes zoster
25.6.1913	———	4.3.0.0.0.	- - - - -	
26.8.1913	———	0.0.0.0.0.	- - - - -	

CHAPTER IV.—CONCLUSIONS.

Before estimating the value of a report upon a Wassermann test, the physician should be acquainted with the methods and general results of the serologist who gives the report.

From the results of the technique described above, the following general conclusions may be drawn:—

(1) In general diagnostic work, exclusive of nervous conditions, a positive reaction is so constant in active syphilis that such a diagnosis, made in the face of a negative result, will require very special support on other grounds before it can be considered probable.

(2) A positive reaction in the cerebrospinal fluid indicates a syphilitic lesion of the central nervous system.

(3) In active untreated cases of dementia paralytica, tabes dorsalis, and cerebrospinal syphilis, the reaction is positive both in the serum and cerebrospinal fluid. In cerebral syphilis, without involvement of the spinal cord, the cerebrospinal fluid is usually negative. Except in the latter cases the strength of the reaction has no certain diagnostic value.

(4) The reaction is apt to be negative in the serum or cerebrospinal fluid in cases of hemiplegia, non-progressive tabes dorsalis, and old lesions of the nervous system, especially in cases of stationary congenital syphilis. It is also usually negative in the serum particularly in very recent nerve lesions of the late secondary period, and in the cerebrospinal fluid particularly in treated cerebrospinal cases.

(5) The occurrence of a positive reaction in one of the test-fluids when the other is negative is so common that a reaction found negative in one fluid only is insufficient to exclude syphilis.

(6) Pure "parasyphilitic" lesions do not respond satisfactorily to treatment as shown by the slight effect upon the reaction in the cerebro-

spinal fluid. Cerebrospinal lesions react very readily to treatment. The celerity with which the reaction in the cerebrospinal fluid responds to treatment is an index of the "parasyphilitic" or "syphilitic" nature of the case.

(7) The positive reaction in the serum is rapidly made negative by treatment in acute syphilis; but in chronic syphilis this effect is produced very slowly. In the cerebrospinal fluid, on the other hand, the rate of reduction of the reaction does not depend upon the duration of the infection. Thus, in gummatous lesions of the central nervous system, as also in acute secondary cerebrospinal syphilis, the effect of treatment upon the reaction in the cerebrospinal fluid is rapid.

(8) The "provocative" injection of salvarsan for the purpose of exciting an exacerbation of the reaction has some, but probably an exaggerated, diagnostic value.

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ON THE BULBAR NUCLEI, WITH SPECIAL REFERENCE TO THE EXISTENCE OF A SALIVARY CENTRE IN MAN.

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ANATOMICAL observations in man and experimental investigations in the lower animals have provided us with an extensive knowledge of the position and relations of the nuclei of the cranial nerves in the medulla oblongata. The following paper, based upon a case which afforded unusual facilities for such an investigation, cannot claim to do more than confirm our previous knowledge of these nuclei; an attempt, however, will be made to go further and establish the existence of a salivary centre in the medulla oblongata.

Experimental researches of Kohnstamm and Yagita [2, 3, 5, 6] have demonstrated the presence of a salivary centre in the medulla in dogs. These results were obtained by division of the chorda tympani and the nerves to the submaxillary and parotid glands. It is seldom that opportunity is afforded in man of studying the effects of lesions which in their nature and result approximate to those of experimental nerve division in the lower animals. But in July, 1913, a brain and spinal cord were received at the Neurological Institute, Frankfurt-am-Main, from a patient where the isolated character of the lesions reproduced experimental conditions with unusual accuracy. A fracture of the base of the skull inflicted local injury upon the trunks of the vagus, glossopharyngeal, spinal accessory, and hypoglossal nerves, without any lesion in the brain itself. Examination revealed degenerated cells in the nuclei of the injured nerves, thus affording an opportunity of localising the anatomical position of these nuclei in man; but degenerated cells were found also in an unusual situation, the significance of which was at first uncertain. As further discussion will show, I venture to believe that these represent a system of cells analogous to those described in dogs as the nucleus salivatorious. For the following clinical notes of the case I am indebted to Dr. Rollmann, of Essen.

The patient, a miner, received a severe injury in the upper part of

the neck on April 18, 1913. When a careful examination was made a few days later, the following conditions were observed:—

(1) Paralysis of the left side of the tongue.

(2) Paralysis of the left sterno-mastoid and upper part of the left trapezius.

(3) Loss of taste in the whole of the back of the tongue, more marked, however, on the left side.

(4) Paralysis of the left side of the palate. No anæsthesia of the palate could be detected.

(5) Aphonic speech.

By laryngoscopic examination the left vocal cord was seen to be immobile.

(6) Loss of power of swallowing, even for liquids.

In addition to the above symptoms a slight left facial paralysis was observed on the first day after the accident, but this rapidly disappeared. It is also stated that immediately after the accident some question arose as to whether the phrenic nerve was injured or not, but on the following day no paralysis of the diaphragm could be detected. At no time was there any paralysis of the extremities, nor with the exception of the paralysis of the left sterno-mastoid and trapezius muscles was there any limitation of the movements of the neck.

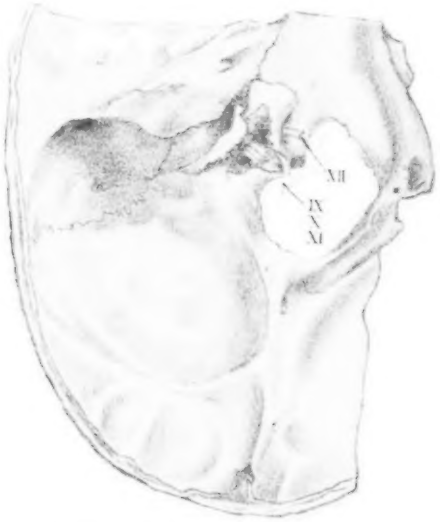
In spite of careful X-ray examination no definite evidence of any fracture was discovered. The fluid obtained by lumbar puncture contained a little blood. A diagnosis of injury to the peripheral roots of the ninth, tenth, eleventh, and twelfth cranial nerves was made. Later observations confirmed those already made; the paralysis of swallowing remained absolute, marked atrophy of the left side of the tongue, and of the left sterno-mastoid and the upper part of the left trapezius followed, the sense of taste was preserved in the right anterior third of the tongue only.

The patient developed bronchitis and broncho-pneumonia, and died on June 28, seventy-one days after the accident.

At the autopsy a fracture of the posterior fossa of the skull was found, involving the jugular foramen. The injured part of the skull was sent for examination together with the brain and spinal cord. An examination of the region of the fracture discloses the following points:—

On the left side the bony ring surrounding the foramen magnum has been fractured in its middle part, in such a way that the circumference of the foramen has been rendered quite irregular. In the situation of

the fracture lie splinters of bone and yellowish red masses of granulation tissue; it is evident that much callus has been thrown out. The anterior condyloid foramen, through which passes the hypoglossal nerve, lies below and in front of the fracture. The fracture has in its lateral part affected the jugular foramen, so that the nerves passing through it are directly involved in the fracture. The brain and spinal cord had been previously hardened in formalin. When examined later the brain appeared normal in general appearance and configuration; no meningitis was present, no naked eye hæmorrhages were visible. The vessels appeared natural. On the left tonsillar lobe of the cerebellum



Sketch to show position of fracture.

was a small area, about 2 c.cm. long by 1 c.cm. broad, where some destruction of tissue had taken place; this was evidently a result of direct pressure from callus or broken spicules of bone. The portions of the cranial nerves remaining attached to the brain showed no visible change. Sections through the brain showed no naked eye lesions.

The cervical part of the spinal cord, the medulla, and the pons were taken, sections cut and stained by Nissl's method, in order to discover the presence of any degenerated cells in the nuclei of the injured nerves. Sections were also stained for the presence of fatty change with Scharlach

red and hæmatoxylin. The material had remained in formalin too long to enable Marchi's method to be used with advantage.

Nissl's method, however, yielded interesting results; evident degenerative changes in the cells could be traced, and in this way the anatomical position of the nuclei concerned could be determined. A glance at the appended diagrams will indicate at once the anatomical position of the degenerated cells. It must be understood that the way in which the cells are depicted, viz., △ for a normal cell and ▲ for a degenerated cell, is purely a convention and bears no relation to the actual size or shape of the cells concerned. This method has only been adopted to

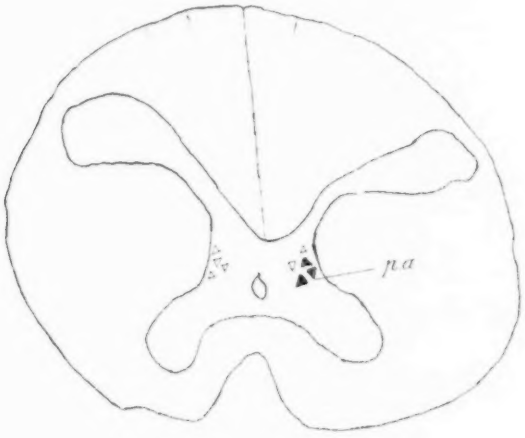


FIG. 1.—*N.a.*, nucleus accessorius.

make the position of the nuclei concerned easily seen; with the same object the diagrams are made as simple as possible.

There is nothing peculiar to record as far as the degeneration itself is concerned. As a rule the number of cells in the affected nucleus seemed reduced; the cells themselves showed the following changes: loss of a clear cell outline; displacement of the nucleus to the periphery of the cell; loss of the typical Nissl granules, with a more diffuse blue coloration of the whole cell substance, and finally, the appearance of numerous parasite glia-cells in and around the degenerated cells.

In the upper part of the cervical cord (see fig. 1) a group of degenerated cells was found lying in the ventro-lateral part of the grey matter of the left side; these cells were quite distinct from the cells in

the ventral horn, which, on the contrary, were well preserved on both sides. They were considered to be cells of origin for the spinal part of the spinal accessory nerve, the degeneration being due to the injury inflicted on the trunk of the nerve in the jugular foramen.

Fig. 2 depicts the appearances observed in a section through the lower part of the medulla, at the level of the decussation of the pyramids. At this level degenerated cells are observed in three groups of cells. One was situated in the grey matter of the left side, dorso-lateral to the central canal, between the central canal and the nucleus

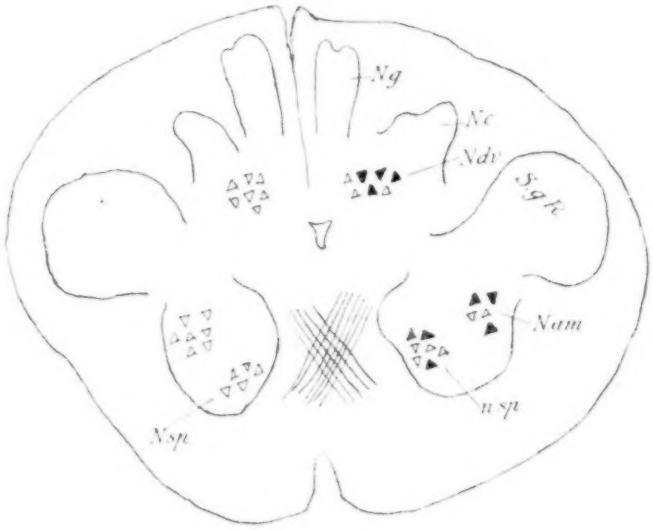


FIG. 2.—*N.g.*, nucleus gracilis; *N.c.*, nucleus cuneatus; *N.d.v.*, dorsal nucleus of vagus; *S.g.R.*, substantia gelatinosa Rolandi; *N.am.*, nucleus ambiguus; *N.sp.*, nucleus supra-spinalis.

cuneatus; only a portion of the cells of this nucleus were degenerated. These cells were regarded as belonging to the dorsal nucleus of the vagus. In the lateral nucleus, the grey matter ventral and internal to the substantia gelatinosa Rolandi, a situation corresponding to the ventro-lateral region of the grey matter of the cord, a second group of degenerated cells were visible. These cells are in all probability those of the lower part of the nucleus ambiguus, the ventral motor nucleus of the vagus group of nerves. Internal to these cells was a third and

smaller group of cells, showing similar evidence of degeneration; this group is probably identical with that described as the "nucleus supra-spinalis" (Jacobsohn [1]), which is stated to lie in proximity to the nucleus of the spinal accessory nerve below, while higher up it comes into relation with the nucleus of the hypoglossal. As the nucleus of the hypoglossal is not visible in the sections under discussion, it seems reasonable to conclude that these cells have given origin to fibres which join the roots of the spinal accessory nerve.

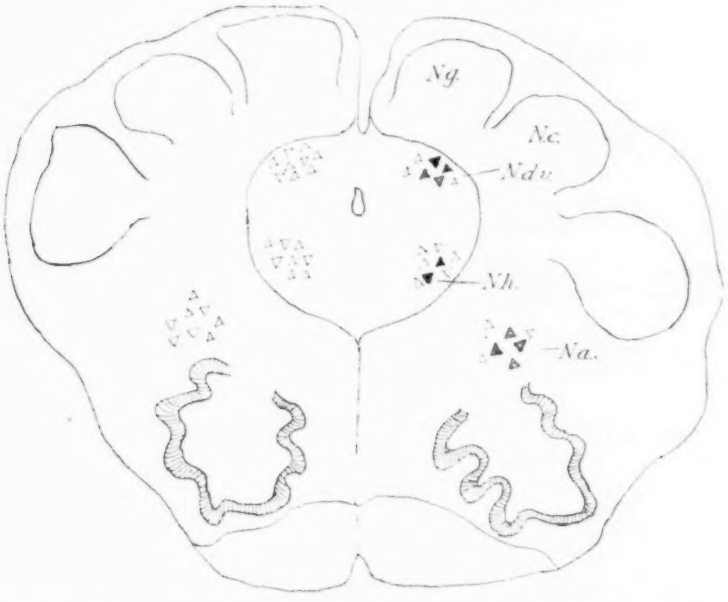


FIG. 3.—*N.g.*, nucleus gracilis; *N.c.*, nucleus cuneatus; *N.d.v.*, dorsal nucleus of vagus; *N.h.*, hypoglossal nucleus; *N.a.*, nucleus ambiguus.

Fig. 3 represents a section through the medulla oblongata at a higher level, where the inferior olives have just become developed. Here again degenerated cells are visible in three groups of cells. In the grey matter round the central canal, and lying dorso-laterally to it, degeneration is again visible in the dorsal nucleus of the vagus. The nucleus of the hypoglossal now comes into view, lying in the grey matter ventro-lateral to the central canal; many of its cells are degenerated. At this level degeneration again appears in the nucleus

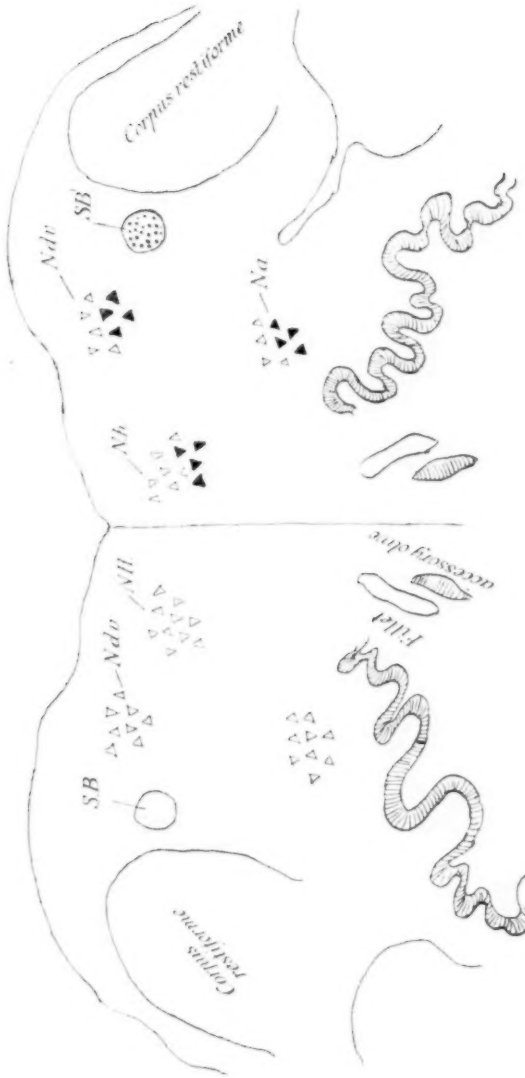


FIG. 4.—*S.B.*, solitary bundle; *N.d.v.*, dorsal nucleus of vagus; *N.h.*, hypoglossal nucleus; *N.a.*, nucleus ambiguus.

ambiguus, which lies in the grey matter ventrally and laterally to the central canal and the hypoglossal nucleus, and just dorsal to the inferior olive.

It will therefore be seen that sections through the lower and middle part of the medulla exhibited a fairly constant picture of localized cell degeneration.

Fig. 4 depicts a section through the upper part of the medulla, cutting through the restiform body at the level of the entrance of the cochlear nerve. Degenerated cells can be seen in the same groups of cells. Owing to the central canal having opened out into the fourth ventricle, the hypoglossal nucleus is placed more dorsally in the grey matter in the floor of the fourth ventricle; here degenerated cells are found in the ventral part of the nucleus only. Lying more laterally and dorsally is the dorsal nucleus of the vagus, of which some cells are degenerated. Just external to this again is the solitary bundle, which in sections stained with Scharlach red shows most striking fatty change. Except for a few scattered points fatty changes were not found elsewhere. The nucleus ambiguus is still visible, and contains degenerated cells.

Fig. 5 is a section at the uppermost part of the medulla. At this level the nucleus of the hypoglossal, the dorsal nucleus of the vagus, and the nucleus ambiguus have disappeared, but some scattered degenerated cells are visible on both sides. They lie in the grey matter just dorsal to the inferior olive, internal and slightly ventral to the facial nucleus. Fig. 6 shows a more detailed view of these cells. The exact significance of this degeneration would be a little uncertain if the experimental researches of Kohnstamm and Wolfstein [4] and Yagita and Hayama [6] had not thrown some light on the question. Kohnstamm [2, 3] has described in dogs a system of large cells which showed Nissl degeneration after cutting the lingual nerve and nerve to the submaxillary gland; this system of cells, which he calls the "nucleus salivatorius superior," lies at the junction of the medulla with the pons, just dorsally to the facial nucleus. The cells extended from the caudal end of the facial nucleus to the frontal end of the trigeminal nucleus; some of the cells were scattered over a wide area, reaching the raphe mesially, Deiters' nucleus laterally, and the floor of the fourth ventricle dorsally. After a unilateral lesion degenerated cells were found on both sides. It has further been observed that affection of the parotid secretion follows cutting of the glosso-pharyngeal nerve, and Kohnstamm described a caudal prolongation of the nucleus salivatorius,

fibres from which pass out with the glosso-pharyngeal nerve; the cells of origin of these fibres lay in the ventral part of the medulla between the inferior olive and the nucleus ambiguus, beginning above at the caudal end of the facial nucleus. To this latter group of cells Kohnstamm gave the name "nucleus salivatorius inferior," and considered that the two together form a centre for the innervation of the salivary glands. By Marchi's method he was able to trace fibres from the nucleus as far as the submaxillary ganglion.

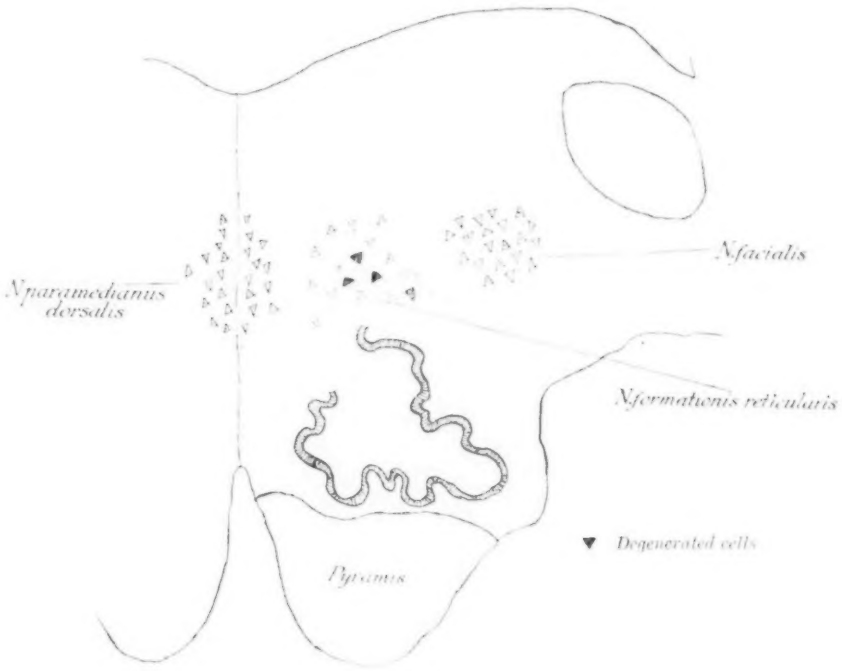


FIG. 5.

Yagita and Hayama [6] cut the tympanic branch of the glosso-pharyngeal nerve in dogs and found degeneration in the situation of Kohnstamm's inferior nucleus. Scattered degenerated cells were also found in the grey matter of the formatio reticularis of this region, in a situation slightly more ventral and mesial than the nucleus already described.

Yagita [5] considered that the secretory centre of the parotid is

a direct caudal prolongation of the nucleus salvatorius lying in the formatio reticularis at the level of the most caudal part of the facial nucleus. The position of the degenerated cells found in my sections corresponds to the scattered degeneration described by Kohnstamm and Yagita. In my sections they are seen to extend from about the level of the entry of the cochlear nerve below to the termination of the inferior olive above; they are not, however, present in every section, and cannot be said to constitute a definite nucleus. In view of the experimental observations quoted, I would suggest that these cells

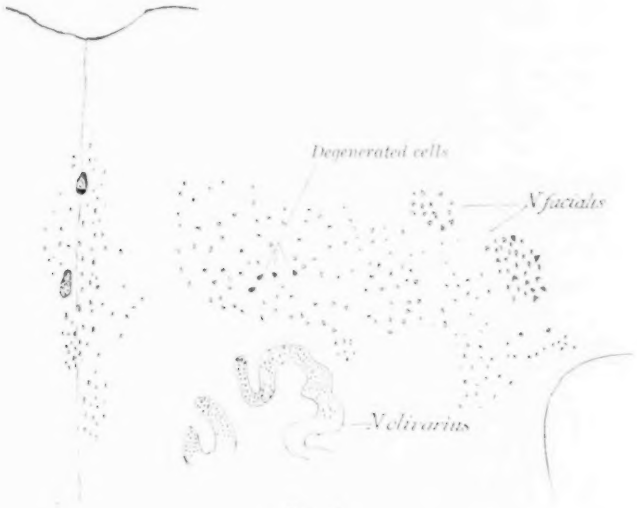


FIG. 6.

represent cells of origin for the secretory fibres which pass out with the glosso-pharyngeal nerve, and which subsequently, by means of its tympanic branch, become distributed to the parotid gland. Unfortunately no clinical evidence was forthcoming as to the presence of any disturbance of salivary secretion; owing to the paralysis of swallowing, the saliva simply dribbled from the mouth, and the explanation of the degenerated cells found is based upon the similar appearances found in dogs. Further observations may perhaps confirm the existence of a salivary centre in the human medulla.

The anatomical changes found may be summarized as follows:—

(1) Degeneration in the cells of origin of the spinal accessory nerve

in the ventro-lateral part of the grey matter of the upper cervical region of the spinal cord.

(2) Degeneration throughout the whole length of the nucleus ambiguus.

(3) Partial degeneration of the dorsal nucleus of the vagus.

(4) Partial degeneration of the hypoglossal nucleus.

(5) Marked fatty change in the solitary bundle.

(6) Scattered degenerated cells in the grey matter of the upper part of the medulla, just dorsal to the inferior olive.

It was somewhat surprising to find such a small amount of fatty change present, it being practically confined to the solitary bundle. The long time elapsing between the injury and the death of the patient (over two months) is no doubt in part a reason for the limited amount of fatty change present. Since the dorsal nucleus of the vagus, which is largely a sensory nucleus, showed only partial degeneration, we may surmise that perhaps the injury to the nerve took place on the distal side of the ganglion, the degenerated cells representing the motor part of this nucleus. In this case the fatty change in the solitary bundle would represent degenerated fibres from the glossopharyngeal nerve. It was, however, impossible to say at exactly what point in their course through the jugular foramen the nerves were injured.

From the fact, too, that the hypoglossal nucleus showed only partial degeneration, we may assume that the injury to the nerve was not complete, a hypothesis which is borne out by an examination of the skull, for, as will be seen from a reference to the sketch, the fracture did not directly involve the anterior condyloid foramen.

In conclusion, I would like to express my gratitude to Professor Edinger, who not only placed the material at my disposal for examination, but also afforded me invaluable assistance in the interpretation of the anatomical changes found.

REFERENCES.

[1] Jacobsohn. "Über die Kerne des menschlichen Hirnstamms," *Neurol. Centralbl.*, 1909, Bd. xxviii, S. 674.

[2] Kohnstamm. *Anat. Anzeig.*, 1902, Bd. xxi, S. 362.

[3] *Idem.* "Vom Centrum der Speichelsekretion, etc.," *Verhandl. des XX Cong. f. inn. Med.*, 1902, S. 361.

[4] Kohnstamm und Wolfstein. "Versuch einer physiolog. Anatomie der Vagusursprünge und des Kopfsympathicus," *Journ. für Psychol. u. Neurol.*, 1907, Bd. viii, S. 177.

[5] Yagita. "Weitere Untersuchungen über die Speichelsekretion," *Anat. Anzeig.*, 1909, Bd. xxxv, S. 70.

[6] Yagita und Hayama. "Über das Speichelsekretioncentrum," *Neurol. Centralbl.*, 1909, Bd. xxviii, S. 738.

Publications Recently Received.

[*Notes on a book under this heading do not preclude a subsequent review.*]

Behandlung der angeborenen und erworbenen Gehirnkrankheiten mit Hilfe des Balkenstiches. Von Professor G. Anton und Professor F. G. von Bramann. S. 188, mit 44 Abbildungen und 10 Tafeln. Berlin: Karger, 1913.

The authors recount five years' experience of the operation of "Balkenstich," on a large number of cases. As the free communication between the ventricles and the subdural spaces of the brain and cord, which is necessary for the proper circulation and nutrition of the brain, is often blocked, they have attempted to make an artificial communication through the corpus callosum. Through a small opening 1½ to 2 cm. behind the coronal suture and the same distance from the middle line, a blunt round-ended cannula with lateral openings is introduced between the hemispheres and passed along the falx cerebri, through the corpus callosum into the anterior horn of the lateral ventricle. When the ventricle has been drained to the extent required, the opening into it is enlarged, and then, according to the authors, generally remains patent.

The effects of this operation in a large number of cases of hydrocephalus, cerebral tumours, hypophyseal tumours, epilepsy, &c., are fully described. No death or serious accident could be attributed to the operation in any of the fifty-three cases on which the authors performed it, and in all in whom the intracranial tension was increased, considerable relief was obtained.

Contribution à l'Étude anatomo-clinique des Monoplegies d'Origine corticale. Par le Dr. M. Regnard. Pp. 216, with 12 plates. Paris: Vigot Frères, 1913.

This monograph is based on the examination of ten cases, supplemented by a diligent compilation of similar cases published by others; but unhappily these observations were not always abstracted from the original descriptions.

The methods of examination employed, especially in the investigation of sensation, appear to have been relatively complete, but the conclusions add little to our knowledge. The author concludes that the motor centres lie entirely in the precentral and paracentral convolutions, and the individual centres are segmentally arranged within them. The sensory zone occupies

the precentral gyrus, but also extends behind the fissure of Rolando and over part of the parietal lobe. This sensory zone is divided, as is the motor area, into centres corresponding to the different segments of the body, each of which lies at the same horizontal level as, and contiguous to, the corresponding motor centre.

Map-Scheme of the Sensory Distribution of the Fifth Nerve (Trigeminus) with its Ganglia and Connexions. By L. HEMINGTON PEGLER. London: Ballière, Tindall and Cox, 1913.

This is a most successful attempt to represent in a comprehensive though simple manner the relations and distribution of the various branches of the trigeminal nerve, and their connexions and anastomoses with other cranial nerves, and especially with the cervical sympathetic fibres.

In many instances simplified or modern titles have replaced older morphological terms, but the main object of the map is to illustrate the functional relationships of the various branches of the nerve, which must be considered in dealing with the etiology of the neuralgias, headaches and referred pains which so frequently result from irritation of its fibres. It is with this end in view too that insets are attached to the map, the one showing the central (bulbo-pontine) relations of trigeminal fibres to other afferent centres, and consequently the possible distribution of pain referred from them; the other, the relation of the peripheral distribution of the fibres of the three trigeminal divisions to that of the cervical roots.

The functional significance of the ganglia and fibres that make up the peripheral branches of the trigeminal nerve are indicated concisely but clearly on the map, and are dealt with more fully in the analytical tables of the anatomy and physiology of the nerve, and of its ganglia and connexions that are supplied with it.

The map, which measures 49 by 59 in., has evidently been designed with extraordinary care and accuracy, and incorporates the latest and most trustworthy knowledge on its subject. It will be found extremely valuable to anatomists in teaching the complicated relations of this nerve, and especially to clinicians in elucidating and studying the seat and extent of the referred headaches and pains so commonly due to affection of its fibres in the skull, face, mouth, nose or ears.

Arbeiten aus dem Pathologischen Institut der Universität Helsingfors, herausgegeben von Professor E. A. HOMÉN. Neue Folge, 1ter Band, 1tes und 2tes Heft. Jena: Fischer, 1913.

These parts of the first volume of a new series edited by Homén contain a number of valuable papers, chiefly on the pathology and pathological anatomy of the nervous system.

Homén himself contributes an elaborate paper on the origin and develop-

ment of cerebral abscesses, and the nature of the cells that are found in and around them; Wallgren writes on the finer histological changes in poliomyelitis and insists on its inflammatory nature and the important part the glia-cells play in it; Fabritius has an interesting clinical and pathological paper on acute myelitis and spontaneous hæmatomyelia, and also describes the histological features of a case of sclerotic atrophy of one hemisphere of the brain; and Silfvast deals with the clinical and pathological characters of tumours at the base of the brain in the region of the hypophysis.

Handbuch der Nervenkrankheiten im Kindesalter. Von Professor L. Bruns, Professor A. Cramer, Professor Th. Ziehen. S. 980, mit 189 Abbildungen im Text und 3 Tafeln. Berlin: Karger, 1912.

The three authorities on nervous disease have described in this work all those affections of the nervous system which can occur in children. The sections vary greatly in completeness, some form short, admirably written monographs, others follow more the style of a text-book. This handbook will be of value to all who are interested in the diseases of childhood. It is profusely illustrated.

Leitfaden der Elektrodiagnostik und Elektrotherapie für Praktiker und Studierende. Von Dr. Toby Cohn. Vierte vollständig umgearbeitete und vermehrte Auflage. S. 212, mit 6 Tafeln und 65 Abbildungen. Berlin: Karger, 1912.

This excellent little handbook has passed into a fourth edition, but though there are many additions, it retains its previous form. It forms a complete guide to the use of electricity in diagnosis and treatment.

Freud's Theories of the Neuroses. By Dr. Eduard Hitschmann (Vienna). Translated by Dr. C. R. Payne. Nervous and Mental Disease Monograph Series, No. 17. Pp. 154. New York: Journal of Nervous and Mental Diseases Publishing Company, 1913.

In this book the author gives a systematic exposition of the views of Professor Freud, who has revised the work throughout. Each chapter is devoted to one aspect of his psychology, especially in relation to functional nervous disorders. In many cases direct quotations are made from Freud's writing, but the whole gains a coherence which is of necessity absent from the originals. The translation is remarkably good, especially in view of the extreme difficulty of the German, and the complexity of the new terms introduced by Freud.

Ueber Nervöse Entartung. Von Professor Dr. OSWALD BUMKE. S. 120. Berlin: Springer, 1912.

Kraepelin defines degeneration as the appearance of inherited qualities, which make it either difficult or impossible for the creature to attain the general aims of life. In mental medicine degeneration signifies a steadily increasing deterioration of the state of nervous health. These complicated questions are dealt with in this work from consideration of our present day knowledge, without special research or investigation of records, and the author concludes that Germany at any rate is not decadent. The general prevalence of functional nervous disorders is simply the result of the social conditions.

Acute Poliomyelitis. By Dr. IVAN WICKMAN (Stockholm), translated by Dr. J. W. J. A. M. MALONEY. Pp. 135. New York: Journal of Nervous and Mental Diseases Publishing Company, 1913.

This is an excellent translation of Wickman's work noticed in BRAIN, vol. xxxv, p. 191. It is far the best summary account we possess of our knowledge of this disease. The plates are admirably reproduced.

Die Gesche Gottfried, eine Kriminalpsychologische Studie. Von Dr. L. SCHOLZ. S. 160, mit 6 Abbildungen. Berlin: Karger, 1913.

The heroine of this extraordinary story was born in 1785 in Bremen, and was executed in 1831, after having poisoned innumerable persons with arsenic. Among her victims were her parents, both her husbands, her children, her devoted servant and several of her most intimate friends. On one occasion she started for a visit provided with rat-paste. She was universally beloved, especially on account of the wonderful devotion she showed in nursing her victims. Her ambition was in every case to kill extremely slowly in order that she might have the pleasure of attending the sick. Documents and portraits are given, and this pamphlet should be in the hands of all who are interested in this remarkable group of criminals.

Dreams and Myths. By Dr. KARL ABRAHAM (Berlin). Translated by WILLIAM A. WHITE, M.D. Nervous and Mental Disease Monograph Series, No. 15. Pp. 74. New York: Journal of Nervous and Mental Diseases Publishing Company, 1913.

Freud in a remarkable study analysed the Œdipus story in the light of his psychological views. This book is an attempt to carry such analysis further to explain the Prometheus myth and the stories of Moses, Samson, and other folk-heroes. The time is, however, scarcely ripe for so wide an extension into so uncertain a branch of anthropological knowledge. The translation is well carried out.

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EDITOR.